Medtronic DBS Therapy for Epilepsy

Neurological Devices Panel

March 12, 2010

Sponsor Presentation

Introduction

Presenter	**Nina Graves, PharmD** Epilepsy Program Director Medtronic, Inc.

Disclosures

- Medtronic employee

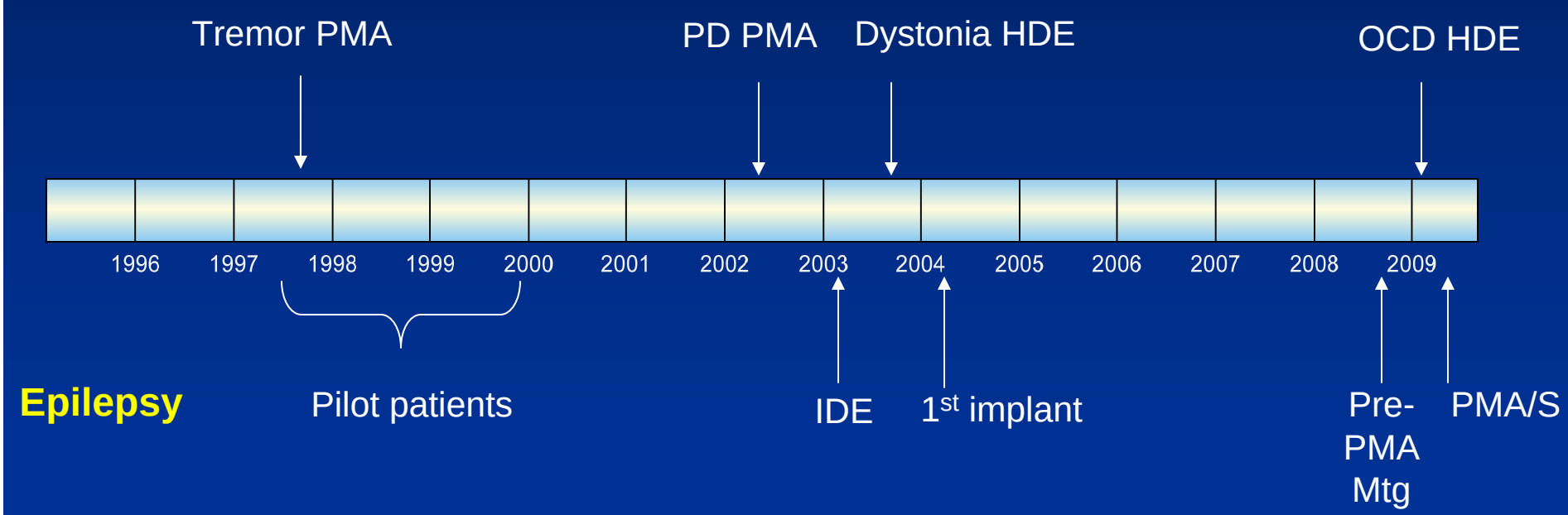
Medtronic DBS Therapy for Epilepsy

- Deep Brain Stimulation (DBS) Therapy for Epilepsy uses an implantable neurostimulator to deliver carefully controlled electrical stimulation to the anterior nucleus of the thalamus (ANT) of the brain, on each side.
- SANTE: Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy

Deep Brain Stimulation (DBS) Therapies

DBS is an approved therapy for several other disease states.

Since 1995, more than 75,000 patients worldwide have received DBS therapy.



Highlights for Advisory Committee Meeting

- Refractory epilepsy is highly prevalent; new therapies are needed.
- Benefit of the therapy was demonstrated in individuals with a long history of epilepsy who had tried and failed most other treatment options.
- Safety profile of DBS therapy acceptable compared to the significant consequences of continued seizures.

Highlights for Advisory Committee Meeting

- FDA has asked you several questions to help them determine the efficacy and safety of this therapy

- We will demonstrate that the reduction in the seizure rate in the active group was statistically significantly greater than in the control group.

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Additional Experts

Neurology	**Douglas Labar, M.D., Ph.D.** Epileptologist SANTE Principal Investigator Cornell University **Vicenta Salanova, M.D.** Epileptologist SANTE Principal Investigator University of Indiana
Neurosurgery	**Michael Kaplitt, M.D., Ph.D.** Neurosurgeon SANTE Investigator Cornell University
Neuropsychology	**Alex Tröster, Ph.D.** SANTE Neuropsychologist University of North Carolina
Quality of Life in Epilepsy	**Joyce Cramer** President, Epilepsy Therapy Project

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Epilepsy Background

Presenter	**Robert S. Fisher, M.D., Ph.D.** Epileptologist SANTE Overall Study Principal Investigator Stanford University Department of Neurology

Disclosures

- SANTE Overall Study Principal Investigator
- Travel expenses compensated by Medtronic

What is Epilepsy?

- A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition[1]
  - The definition of epilepsy requires the occurrence of at least one epileptic seizure
- Clinical manifestations may range from minor sensations to motor convulsions, complex automatic behaviors or full loss of consciousness
- Nature of the disorder
  - Unpredictable; profound impact on daily living, injuries, death
  - Depression and/or anxiety 4 times more likely[2]
  - Other common co-morbidities include cognitive impairment, psychosocial, behavioral and reproductive problems

[1] Fisher et al 2005

[2] LaFrance WC Jr, Kanner AM, Hermann B. Psychiatric comorbidities in epilepsy. Int Rev Neurobiol. 2008;83:347-83.

Seizure Classification

- International League Against Epilepsy (ILAE)
  - Partial onset seizures
    - Simple partial seizures
      - » No decreased consciousness, awareness, or memory
    - Complex partial seizures
      - » Decreased consciousness, awareness, or memory
    - Partial seizures evolving to secondary generalized seizures
  - Generalized seizures
  - Unclassified seizures
- "Most severe" seizure as noted by the subject

Size of Indicated Population

- 2.3 million adults in the US are diagnosed with epilepsy, with 150,000 new cases per year.
- 57% (1.3 million) have partial onset seizures.[1]
- Approximately one third (430,000) are considered refractory as they continue to have seizures and/or intolerable side effects despite optimal medical management.

[1]Hauser et al., Descriptive Epidemiology of Epilepsy: Contributions of Population-Based Studies from Rochester, Minnesota, *Mayo Clin Proc* 1996; 71;576-586

Current Treatments for Epilepsy

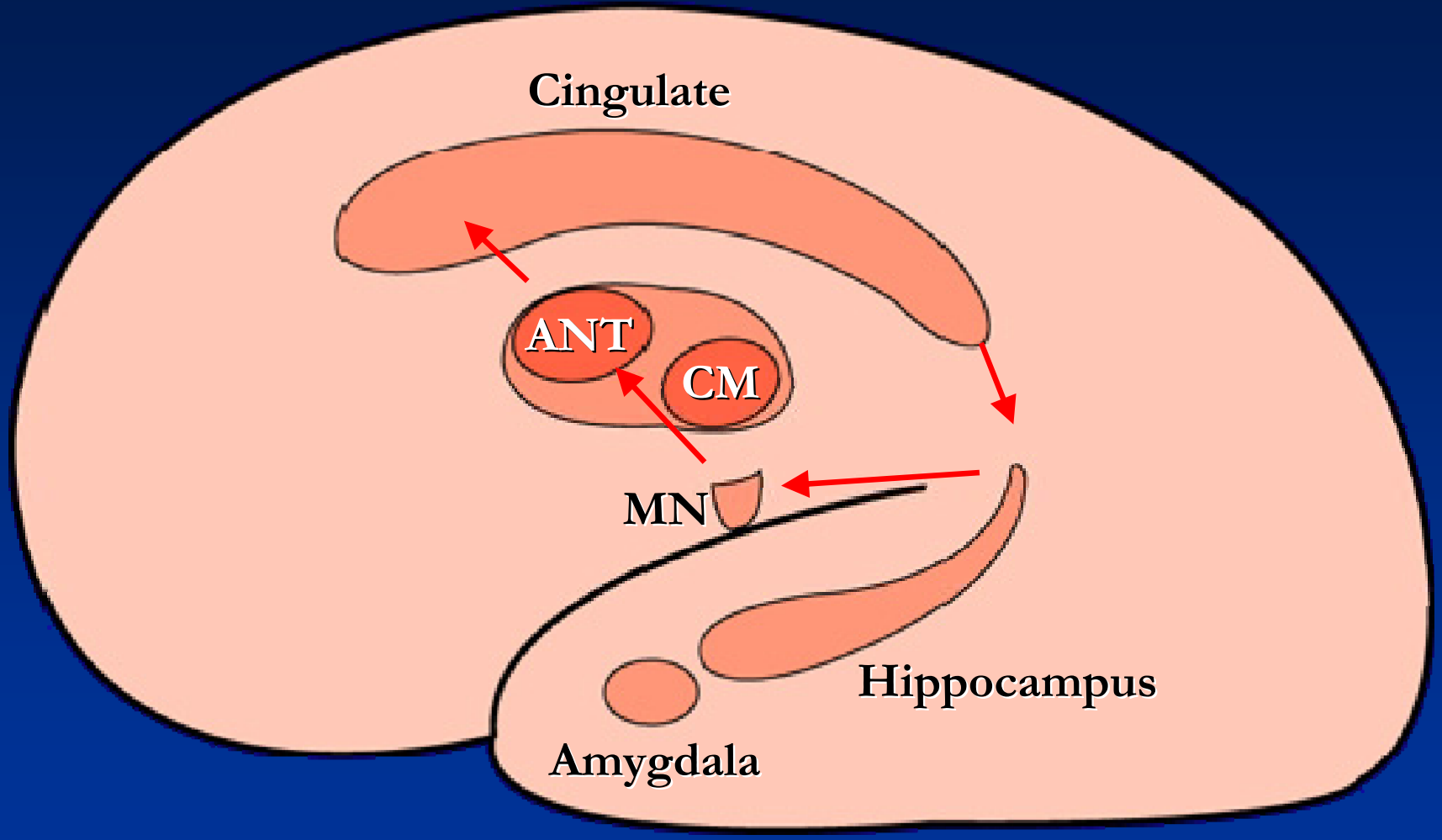
- Pharmacological (antiepileptic drugs or AEDs)
- Surgery
- Ketogenic diet
- Vagus Nerve Stimulation (VNS)
- Other treatments

Rationale for ANT Stimulation

- The ANT is a reasonable stimulation site based on:
  - Anatomical function of this nucleus in a well known brain circuit (Papez), implicated to be involved in seizures.
  - Stimulation of ANT evokes potentials, reduces synchrony, and increases inhibition in hippocampus or neocortex.
  - ANT stimulation was independently assessed in 6 pilot studies in subjects with refractory epilepsy.

Rationale for ANT Stimulation

Neurophysiology: Circuit of Papez



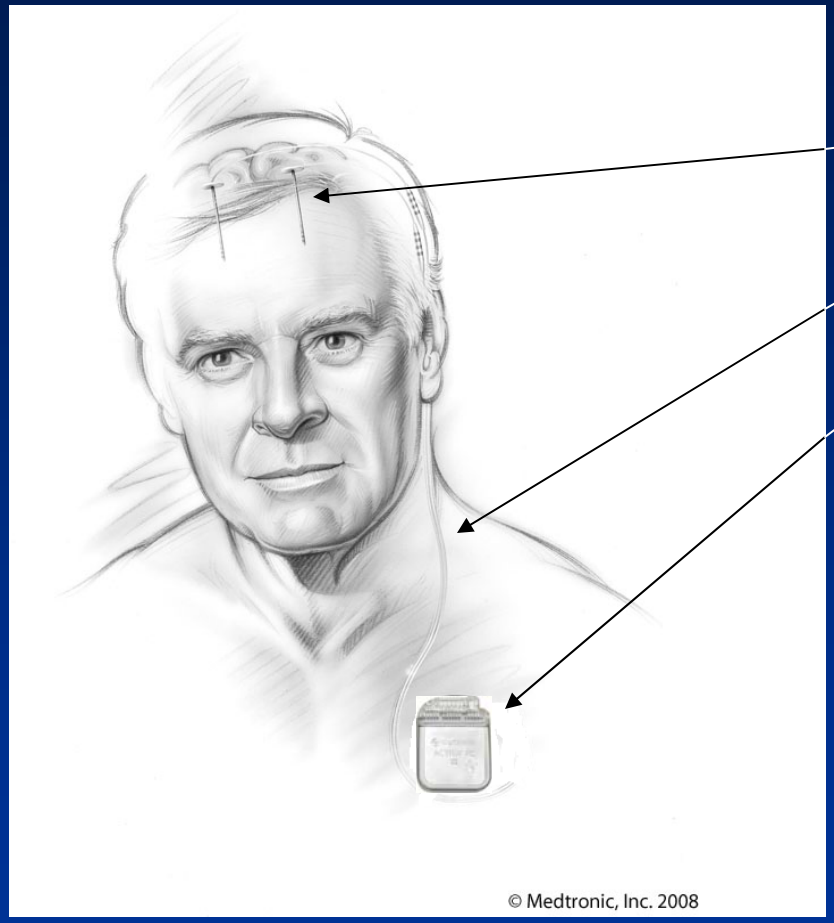
Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Proposed Indication for Use

Bilateral anterior nucleus of the thalamus (ANT) stimulation is indicated as adjunctive therapy for reducing the frequency of seizures in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to antiepileptic medications.

Medtronic DBS System for Epilepsy



Implantable components

Leads

Extensions

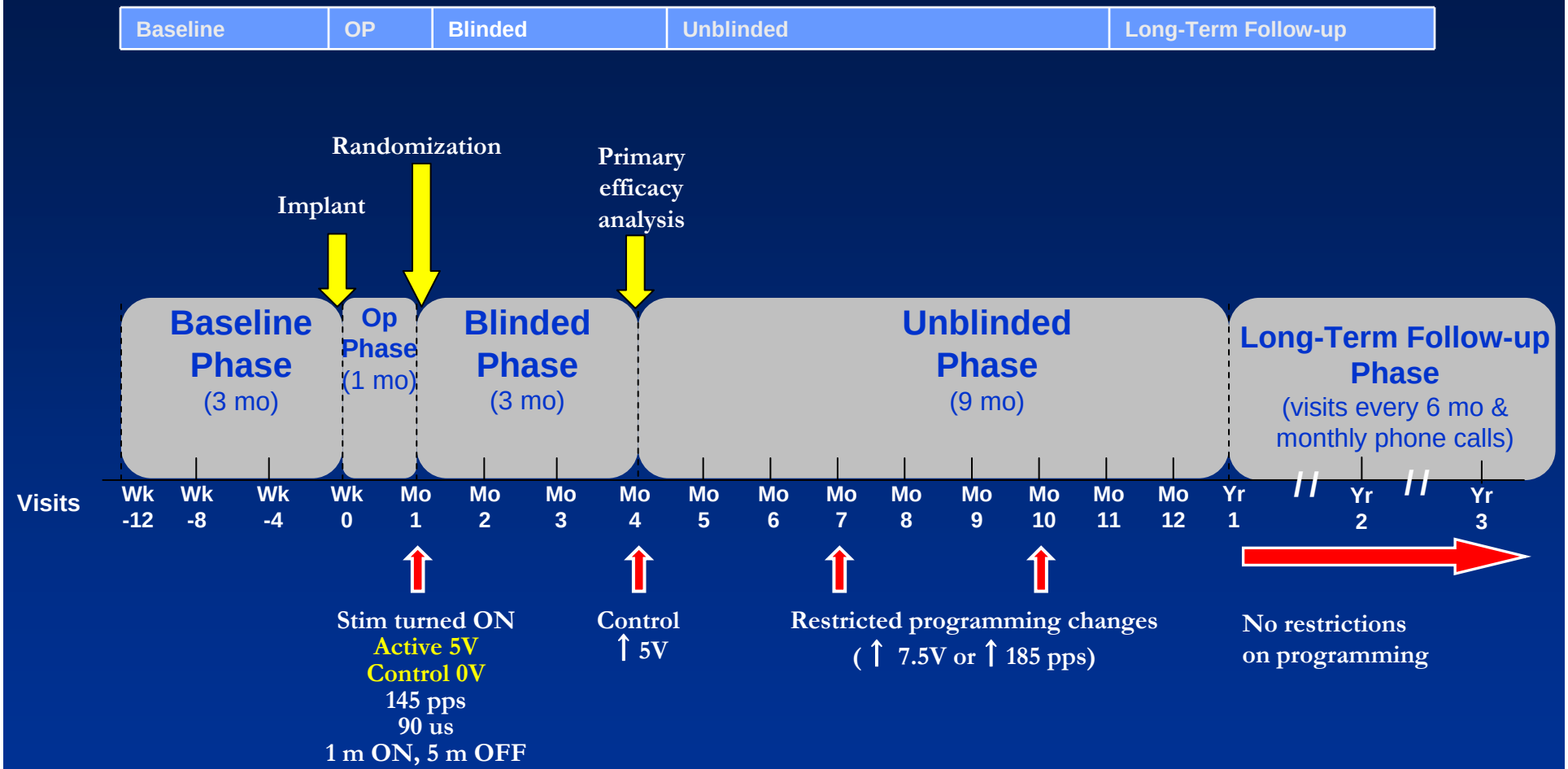
Implantable neurostimulator

Programmers

Clinician programmer

Patient programmer

SANTE Study Design



Objectives

- **Primary Efficacy (Blinded Phase)**
  - To demonstrate that the reduction in seizure rate in the active group is greater than in the control group
- **Secondary (Blinded Phase)**
  - Responder rate
  - Seizure free days and seizure free intervals
  - Treatment failures
- **Additional Study Measures (Blinded Phase)**
  - Seizure type and severity
  - Quality of life (QOLIE)
  - Neuropsychological testing
  - Therapy access controller activations
  - Healthcare resource utilization
  - Rescue medication use
- **Safety**
  - Characterize adverse events
  - Characterize incidence of Sudden Unexplained Death in Epilepsy (SUDEP)

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

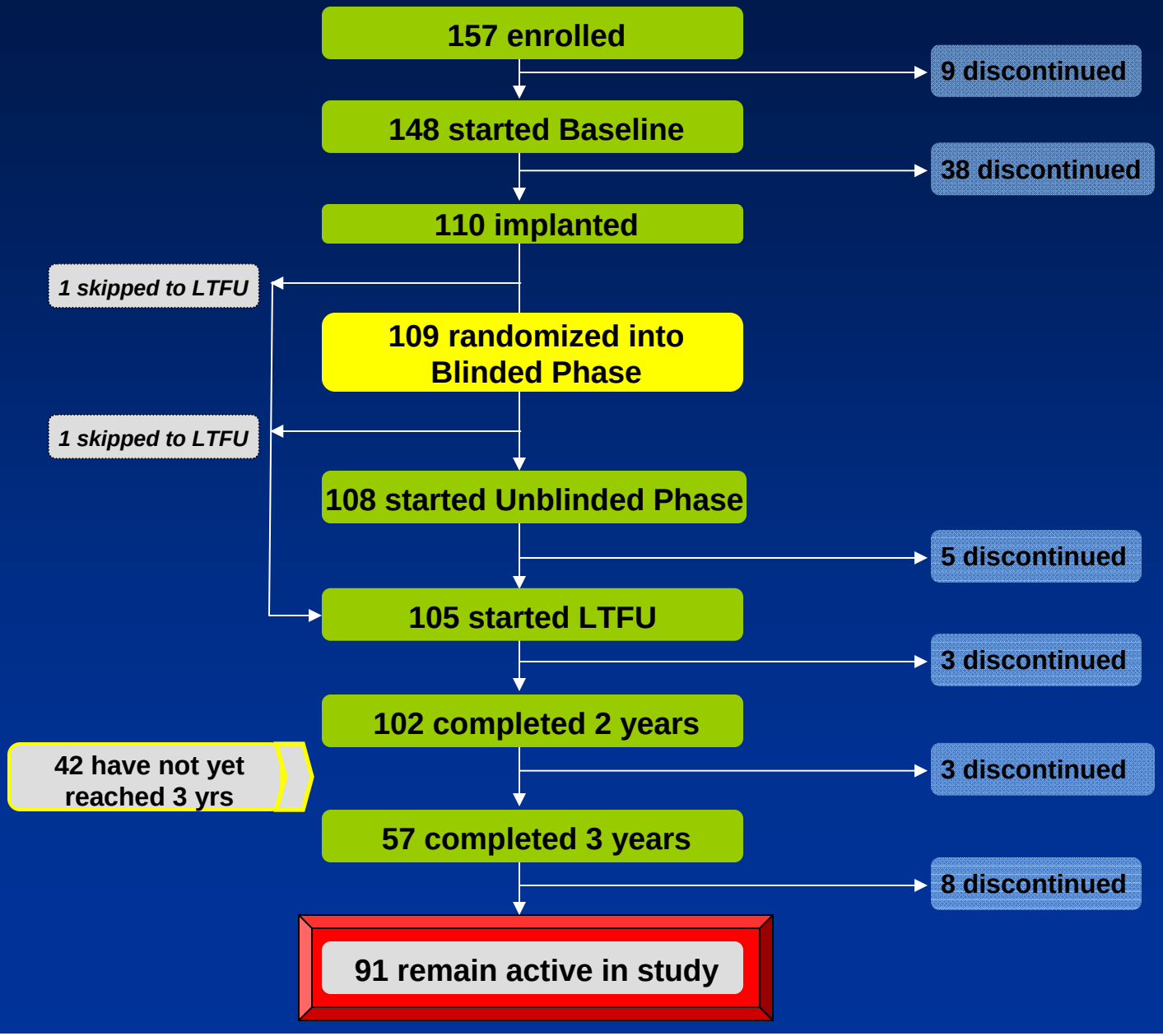
Eligibility Criteria (abbreviated)

- Age 18-65, inclusive
- 6 or more partial seizures with or without secondary generalization per month
- No more than 30 days between seizures in the baseline phase
- Refractory to at least 3 antiepileptic drugs (AEDs), currently taking 1-4 AEDs
- Not a candidate for, or unwilling to undergo, potentially curative resective surgery
- If Vagus Nerve Stimulator (VNS) in place, willing to remove it prior to or at time of DBS implantation
- Suicide attempt or psychiatric illness hospitalization within the 5 years
- Previous diagnosis of psychogenic/nonepileptic seizures

Demographics

Demographic	Total (N=110)	Active (n=54)	Control (n=55)	p-value
Age (mean)	**36.1 years**	35.2	36.8	0.48
Female (%)	**50%**	54%	46%	0.39
Years with epilepsy (mean)	**22.3 years**	21.6	22.9	0.61
Baseline seizure counts per month (median)	**19.5 seizures per month**	18.4	20.4	0.96
Number of epilepsy meds (%):				
1	**10%**	9%	11%	0.29
2	**50%**	48%	51%	
3	**37%**	43%	33%	
4	**3%**	-	6%	
Previous VNS (%)	**45%**	39%	51%	0.21
Previous epilepsy surgery (%)	**25%**	20%	29%	0.29

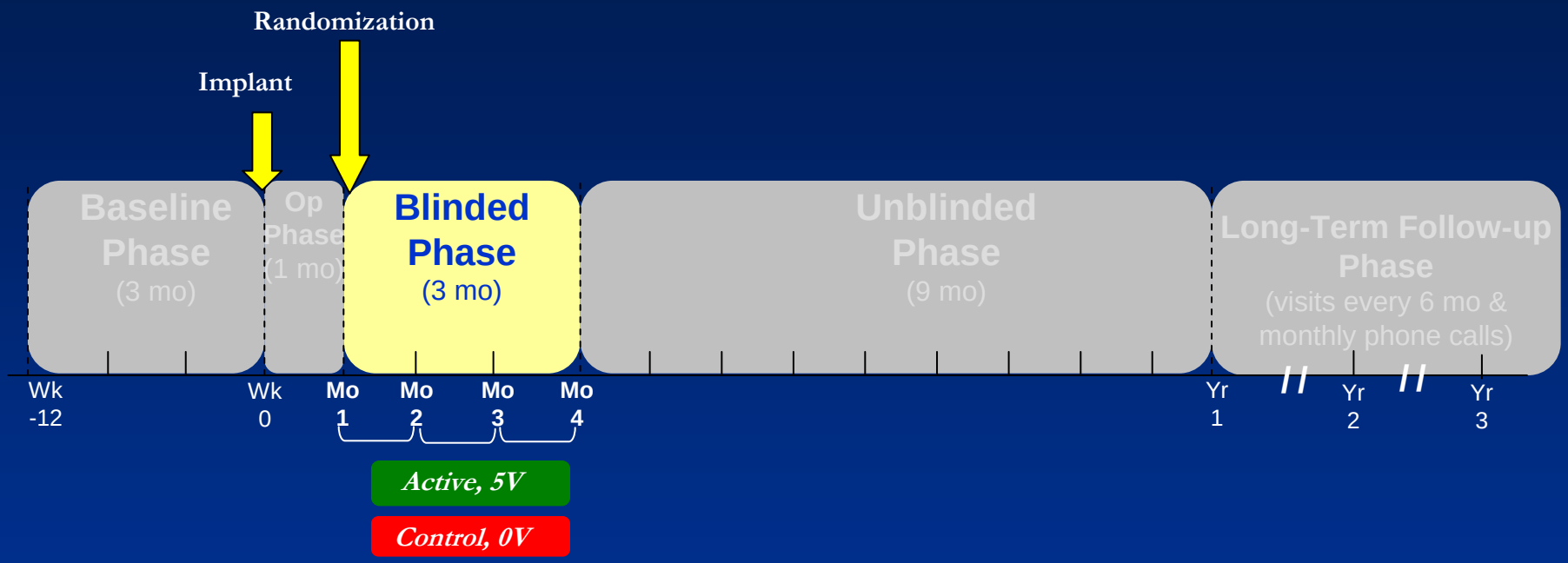
Subject Accountability



Subject Discontinuations

Reason for Discontinuation	Baseline Phase	Blinded Phase	Unblinded Phase	Long-term Follow-up Phase		
				Yr 1-2	Yr 2-3	>Yr 3
Eligibility criteria	24	-	-	-	-	-
Withdrawal of consent (changed mind)	17	-	-	-	1	-
Physician decision	2	-	-	-	-	-
Lymphoma	1	-	-	-	-	-
Device explant (due to AE)	-	-	4	1	2	2
Device explant (due to lack of efficacy)	-	-	-	1	-	4
Death	1	-	1	1	-	2
Other	2	-	-	-	-	-
Total	**47**	**0**	**5**	**3**	**3**	**8**

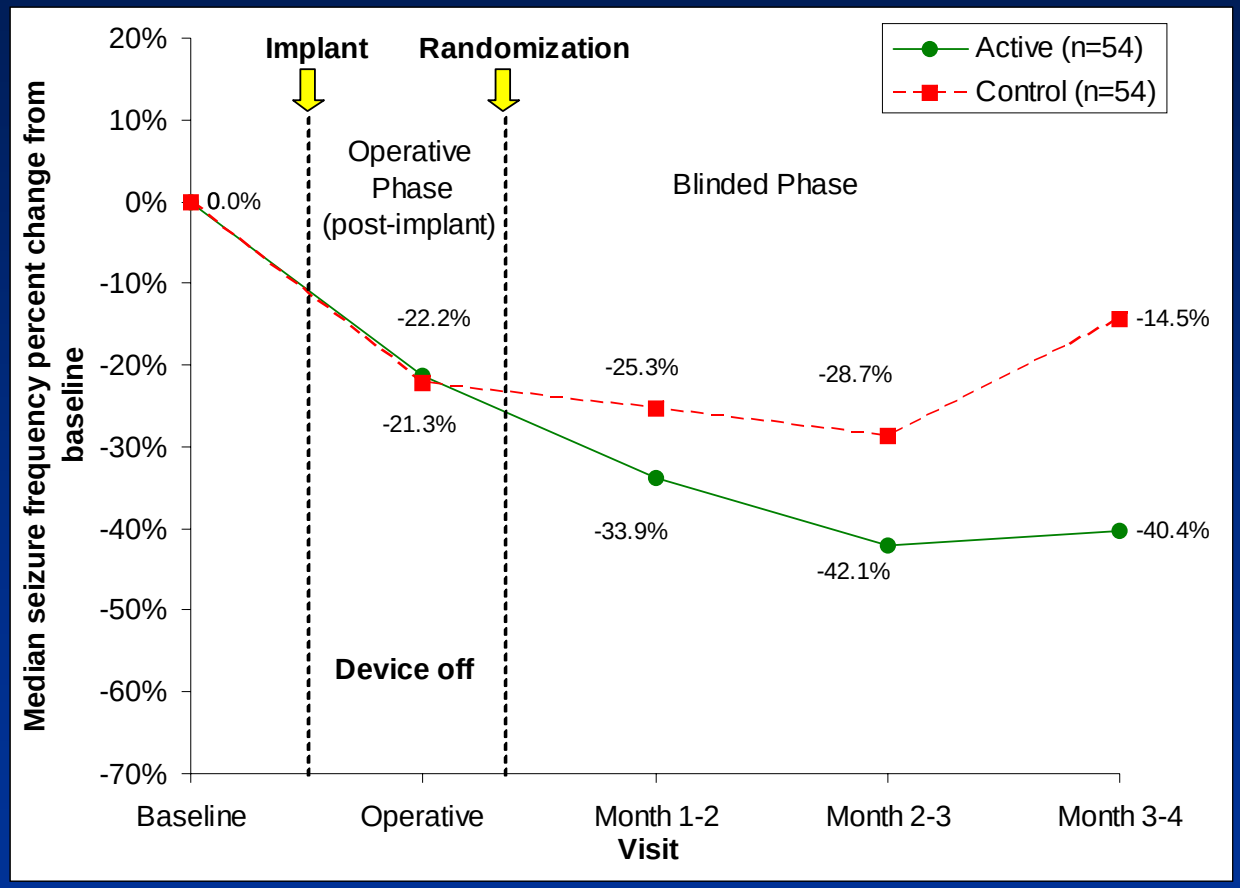
Blinded Phase: Efficacy Results



Median Total Seizure Frequency Reduction

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

- Both groups had a similar drop in the Operative Phase
- The active group continues to improve while the control group trends towards baseline



Discussion of FDA Median Seizure Frequency Analysis

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

- The FDA is asking you to consider median seizure count differences, active vs control, of 2.3 in the Blinded Phase overall and 6.5 in the final month of the Blinded Phase.
- Baseline Phase range of 6 to 604 seizures/month.
- Percent change from baseline is more clinically relevant
- Statistical significance was prespecified to be determined by the GEE analysis.

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Primary Objective Methods and Results

Presenter	**James Rochon, Ph.D.** Department of Biostatistics and Bioinformatics Duke Clinical Research Institute

Disclosures

- Travel expenses compensated by Medtronic
- Consultant for Medtronic

Primary Efficacy Model

- The primary efficacy model described in the protocol is the Generalized Estimating Equation (GEE) model.
  - References: Liang & Zeger[1] and Diggle et al[2].
- Incorporated into PROC GENMOD in SAS.
- Similar to Analysis of Covariance (ANCOVA):
  - Treatment effect, time effect, treatment × time interaction
  - Includes study design factors (e.g., clinical center)
  - Allows baseline covariates which account for variability in the outcome.

[1]Liang K-Y, Zeger SL. *Biometrika* 1986; 73:13-22.

[2]Diggle PJ, Heagerty PJ, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data*. 2nd edn. New York: Oxford University Press; 2002: Chapter 8.

Advantages of the GEE Model

GEE goes beyond ANCOVA in the following manner:

- Allows for longitudinal data from the same subject.
- Provides for a correlation structure among the repeated measures from the same subject.
  - We used the exchangeable correlation structure.
- Allows for unequal time intervals between the observations (e.g., “month”).
  - Estimates are standardized to a “month” of 28 days.
- Provides for data that are not “normally” distributed:
  - The number of seizures tends to be skewed.
  - We used *ln* link and negative binomial distribution.

Primary Objective Analysis

Generalized Estimating Equations (GEE) Model

Prespecified candidate GEE model:

Variables required in final model:

- Treatment effect
- Log of baseline seizure counts
- Offset (number of days in month)

Required

Variables tested (included if p<0.1):

- Treatment by center interaction
- Center

p>0.1

- Treatment by visit interaction
- Visit

p<0.1

- Baseline covariates: gender
- Log of years with epilepsy
- Seizure onset location

p>0.1

- Log of age

p<0.1

Final GEE model:

Treatment effect

Log of baseline seizure counts

Offset

Treatment by visit interaction

Visit

Log of age

= Not included in final model

Primary Objective Presentation

- All primary objective *p*-values are derived from the GEE model.
- Estimated means derived from the GEE model (called least squares means).
- Derived on the *ln* scale; exponentiated back to original scale.
- Treatment Effect: ratio of active to control.
- Value less than 1 implies active is more effective.

Primary Objective Presentation

- Primary
  - At least 70 days of diary in the Blinded Phase
- Alternative
  - Primary with “outlier” subject removed
- Intent-to-treat, alternative
  - At least one day of diary in the Blinded Phase with “outlier” subject removed
    - Adds one control subject with 66 of required 70 days of diary

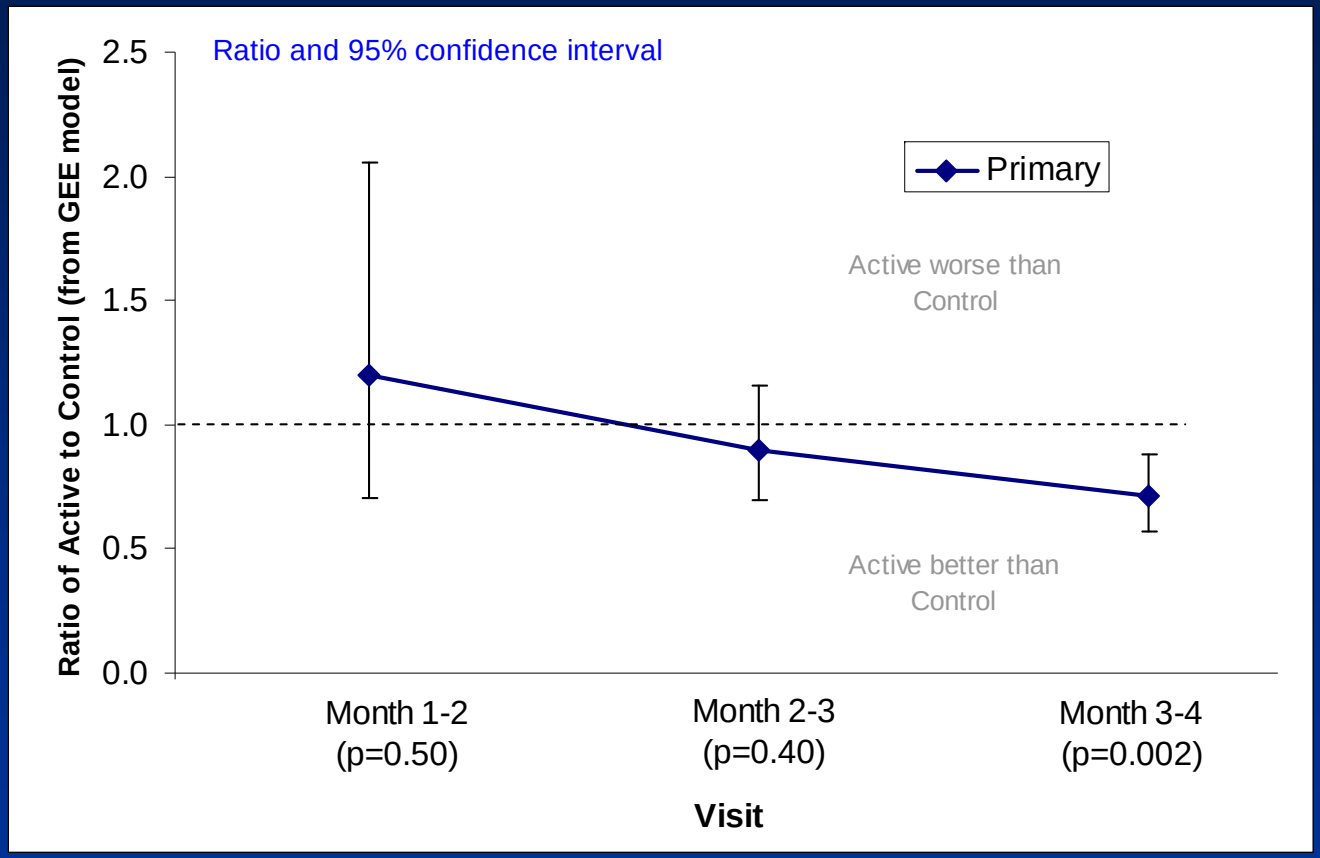
Tests of Significance – Primary Analysis

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

Effect	*p*-value
Treatment	0.4827
Visit	0.0689
Treatment × Visit Interaction	**0.0693**
ln (baseline seizures)	<0.0001
ln (age)	0.0504

Primary Analysis

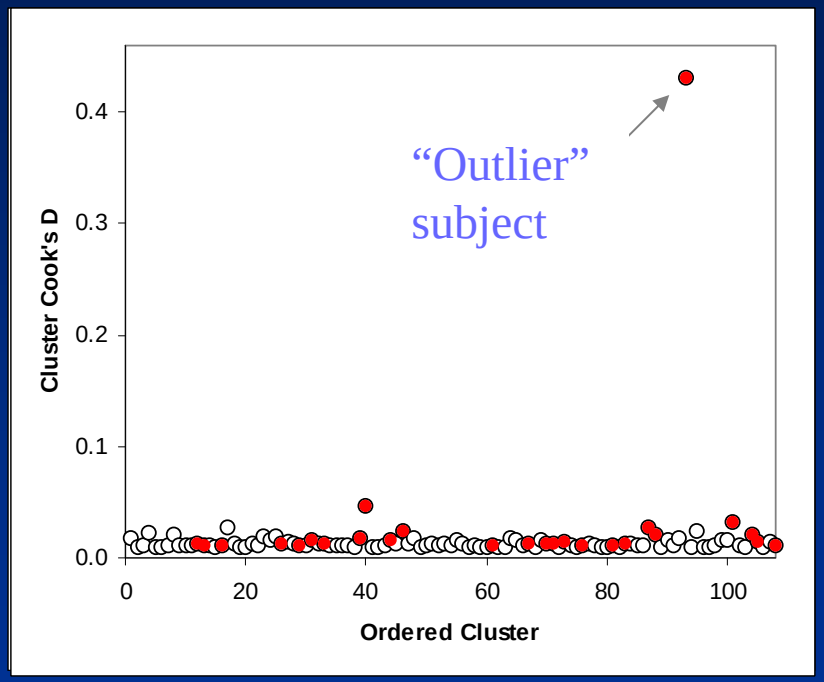
Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

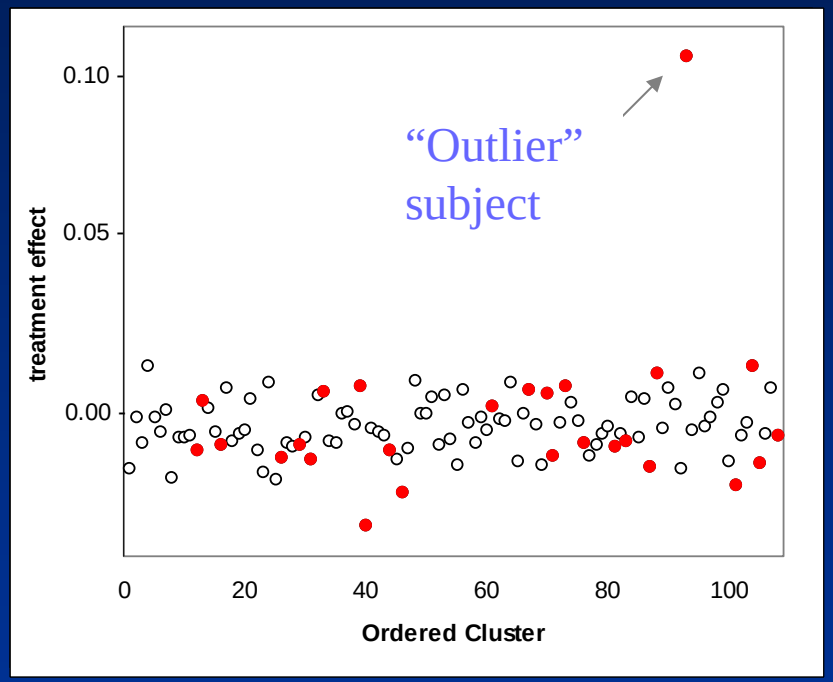


P-value = 0.002 for final month of Blinded Phase

“Outlier” Statistical Rationale

One subject clearly different from all others





Red dot = subjects with an increase in seizures in the Blinded Phase as compared with baseline

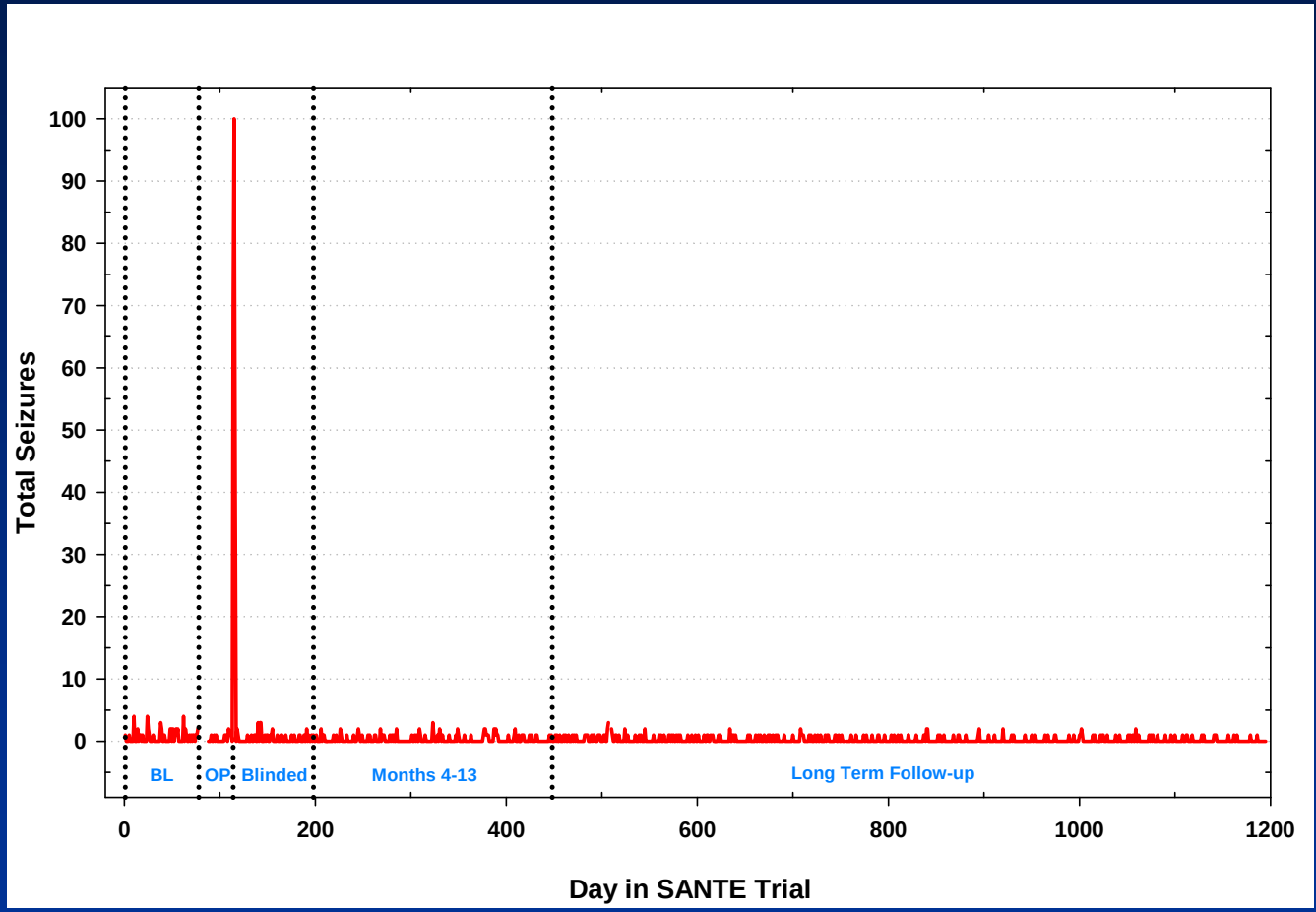
“Outlier” Clinical Rationale

Presenter	**Evan Sandok, MD** Epileptologist SANTE Principal Investigator Marshfield Clinic

Disclosures

- SANTE Study Principal Investigator
- Travel expenses compensated by Medtronic
- Consultant for Medtronic

“Outlier” Clinical Rationale



These seizures have never recurred, even after 9 volts of stimulation in the Long-term Follow-up Phase.

“Outlier” Clinical Rationale

- Acute symptomatic seizures (due to programming):
  - Similar to existing complex partial seizure which is 3.5 minutes long; 30 min post-ictal
  - Significantly shorter duration
  - No EEG confirmation
- Data supporting the unique nature of these events
  - These acute symptomatic seizures resolved after reprogramming (5 to 4 volts).
  - High number partly due to clinic requested re-challenge
  - These acute symptomatic seizures have never recurred even at higher voltages
  - Patient has subsequently done well
- These unique events are not reflective of the spontaneous epileptic seizures that are the focus of therapy

Subject B

- A new non-seizure serious adverse event appeared in month 9 of the study (unblinded phase) and prompted a spontaneous report
- This was diagnosed as a possible conversion disorder, not seizures
- Also, caregiver changed last month of blinded phase
- Seizure count was 23 in the month before and 29 in the month after the change
- Among many suggested sensitivity analyses, removal of this patient was tested, however, clinical review indicates reliable data during the blinded phase
- There is no clinical or statistical reason to discount patient B

Primary Objective Methods and Results

Presenter	**James Rochon, Ph.D.** Department of Biostatistics and Bioinformatics Duke Clinical Research Institute

Alternative Analysis

- Consulted the International Conference on Harmonisation (ICH) E9 Guidance on Statistical Principles
- Section 5.3 “Missing Values and Outliers” suggests
  - “Clear identification of a particular value as an outlier is most convincing when justified medically as well as statistically, and the medical context will then often define the appropriate action. …If no procedure for dealing with outliers was foreseen in the trial protocol, one analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect should be performed and differences between their results discussed.”

Reference: Food and Drug Administration. “International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials; Availability.” *Notice, 63* Federal Register 49583. (September 16, 1998)(FDA *Guidance (ICH:E9): Statistical Principles)*

Tests of Significance – Alternative Analysis

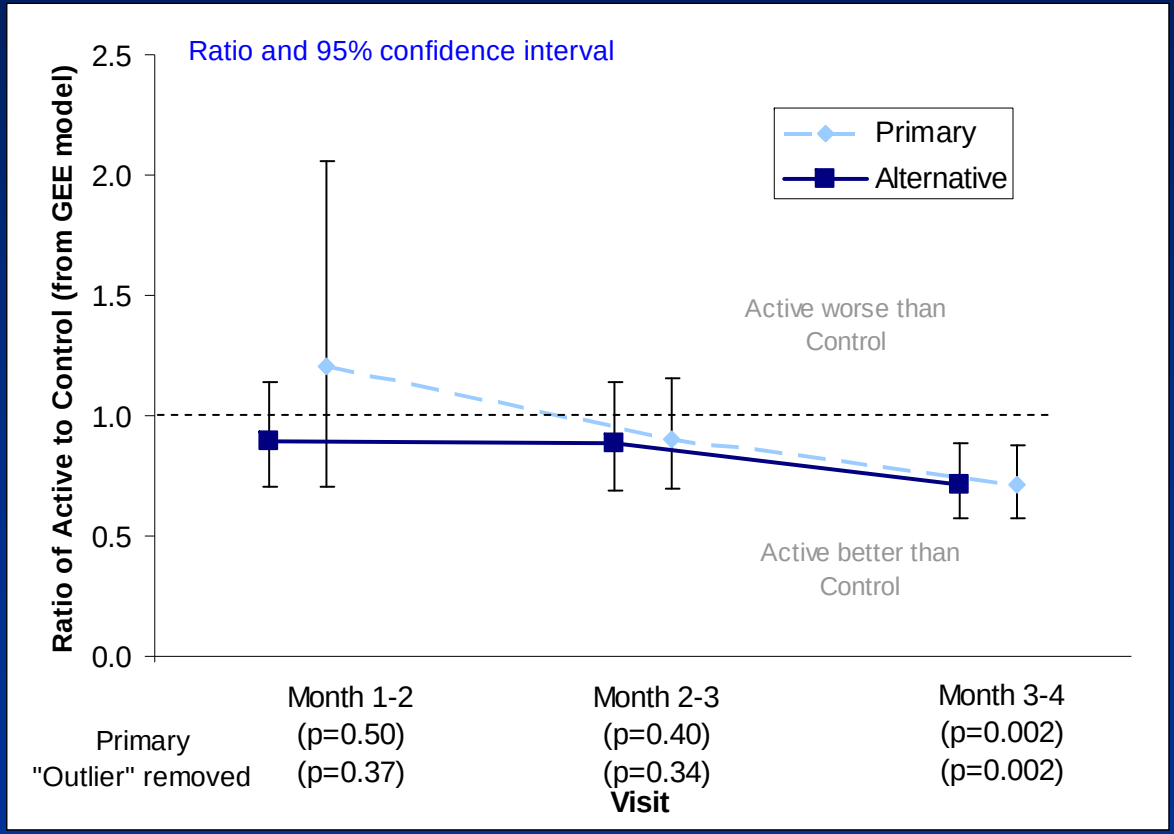
Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

Effect	*p*-value
Treatment	**0.0426**
Visit	0.0310
Treatment × Visit Interaction	0.0960
ln (baseline seizures)	<0.0001
ln (age)	0.0151

Alternative Analysis

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

P-value = 0.04 for the entire Blinded Phase
P-value = 0.002 for final month of Blinded Phase



Tests of Significance – ITT Alternative Analysis

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

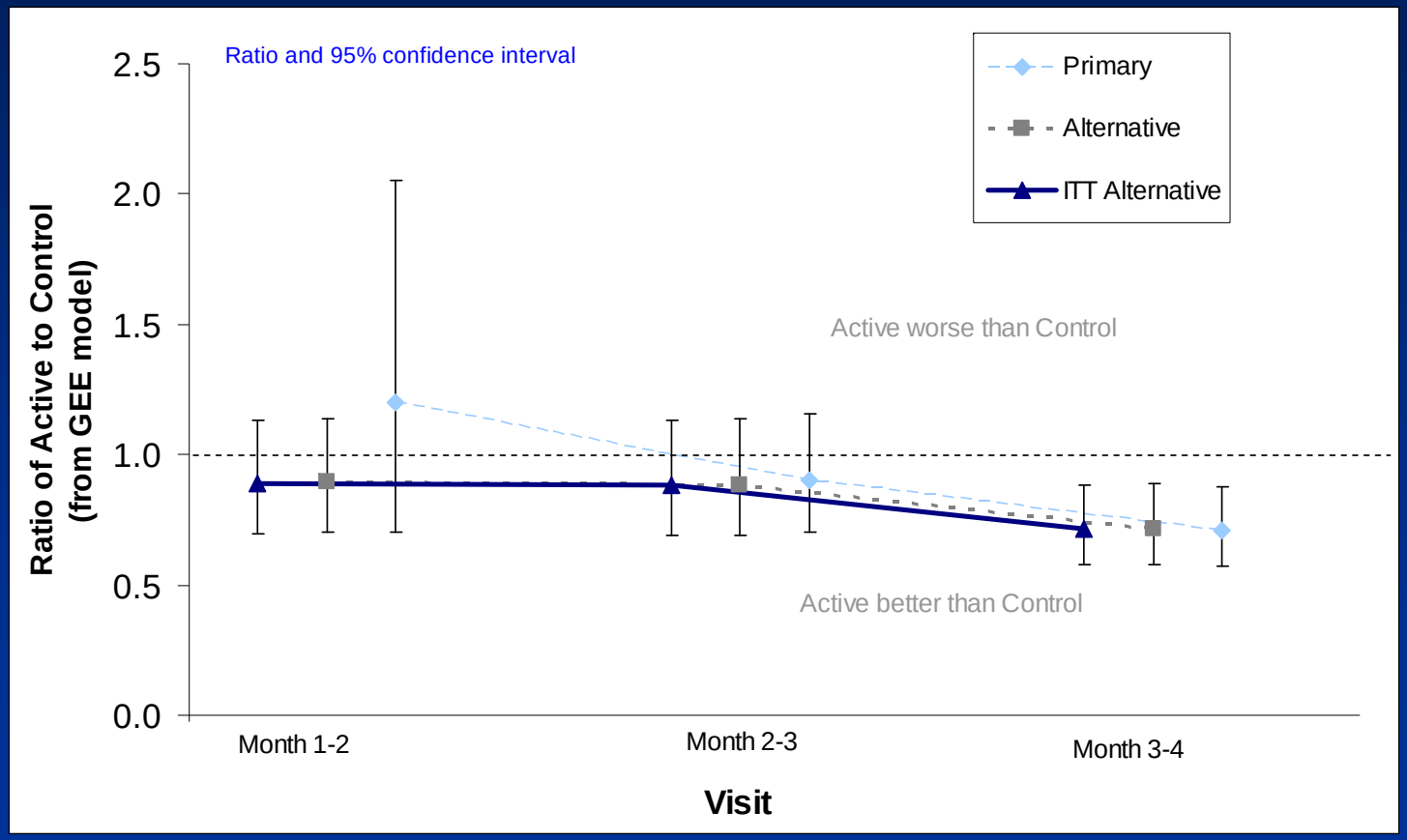
Effect	*p*-value
Treatment	**0.0383**
Visit	0.0252
Treatment × Visit Interaction	0.1029
ln (baseline seizures)	<0.0001
ln (age)	0.0155

ITT Alternative Analyses

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

P-value < 0.04 for the entire Blinded Phase

P-value = 0.002 for final month of Blinded Phase



Sensitivity Analyses

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

- Intent-to-treat
- Per-protocol (no medication changes)
- As treated
  - >95% stimulation ON
  - >80% stimulation ON
- Removal of subject B (with possibly unreliable diary)
- Results:
  - Without the “outlier” (subject ‘A’), virtually* all are statistically significantly different over the entire Blinded Phase
  - With and without the “outlier” (subject ‘A’), all are statistically significantly different in final month of Blinded Phase (all p-values <0.006)

Primary Objective - Summary

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

- The protocol-specified analysis was heavily influenced by an outlier subject.
- Removing the outlier produced a significant treatment effect.
- The ITT analysis with the outlier removed also produced a significant treatment effect.
- All analyses found a significant benefit for the active intervention in the final month of the Blinded Phase.

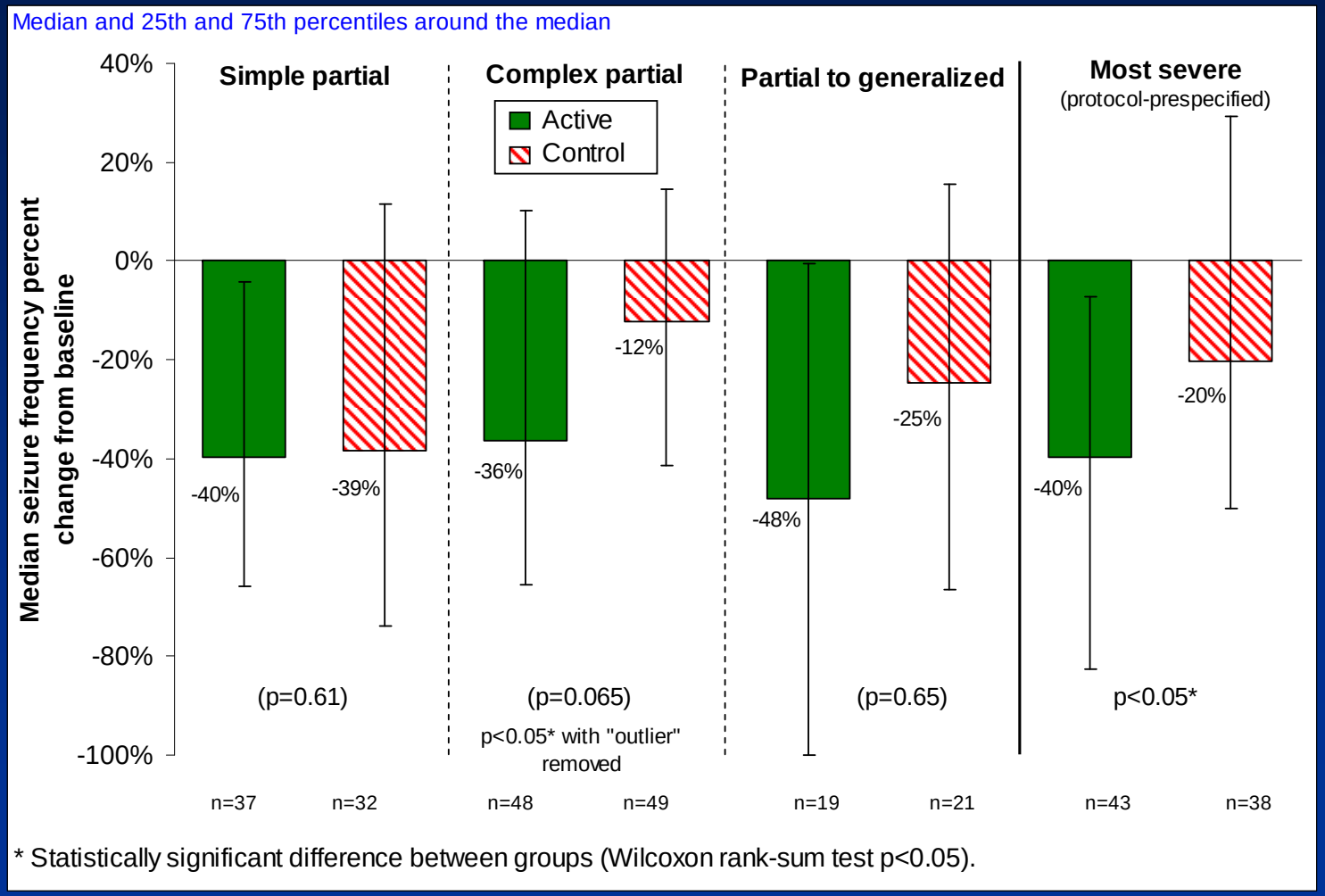
Analysis Method	All Eligible Patients Treatment Effect Wald p-value	"Outlier" Removed Treatment Effect Wald p-value
Primary Analysis	Overall: 0.483 Mo 3-4: 0.0017	Overall: 0.043 Mo 3-4: 0.0023
Intent-to-Treat	Overall: 0.470 Mo 3-4: 0.0016	Overall: 0.039 Mo 3-4: 0.0022

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Seizure Reduction by Seizure Type

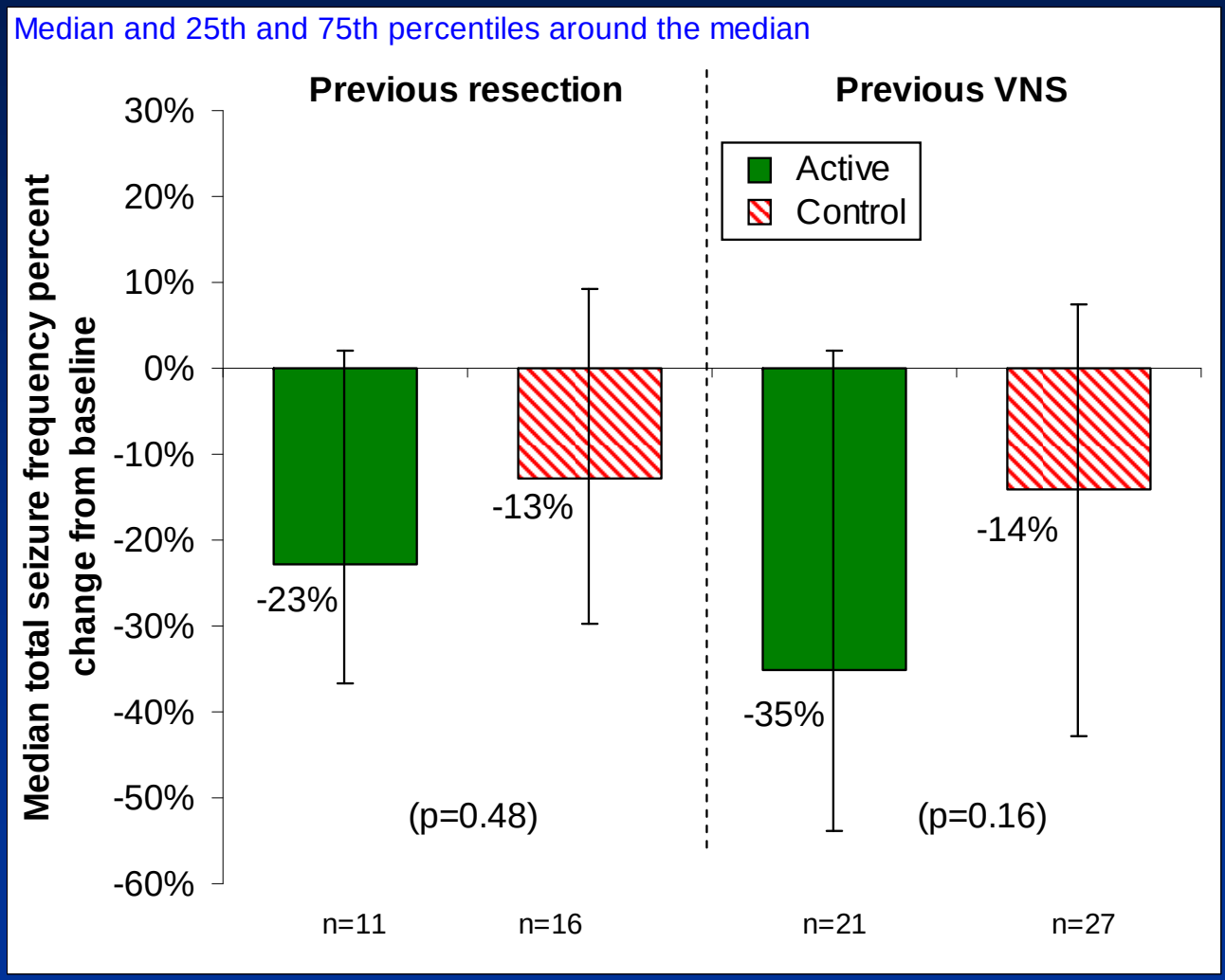
Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up



* Statistically significant difference between groups (Wilcoxon rank-sum test p<0.05).

Seizure Reduction by Previous VNS or Surgery

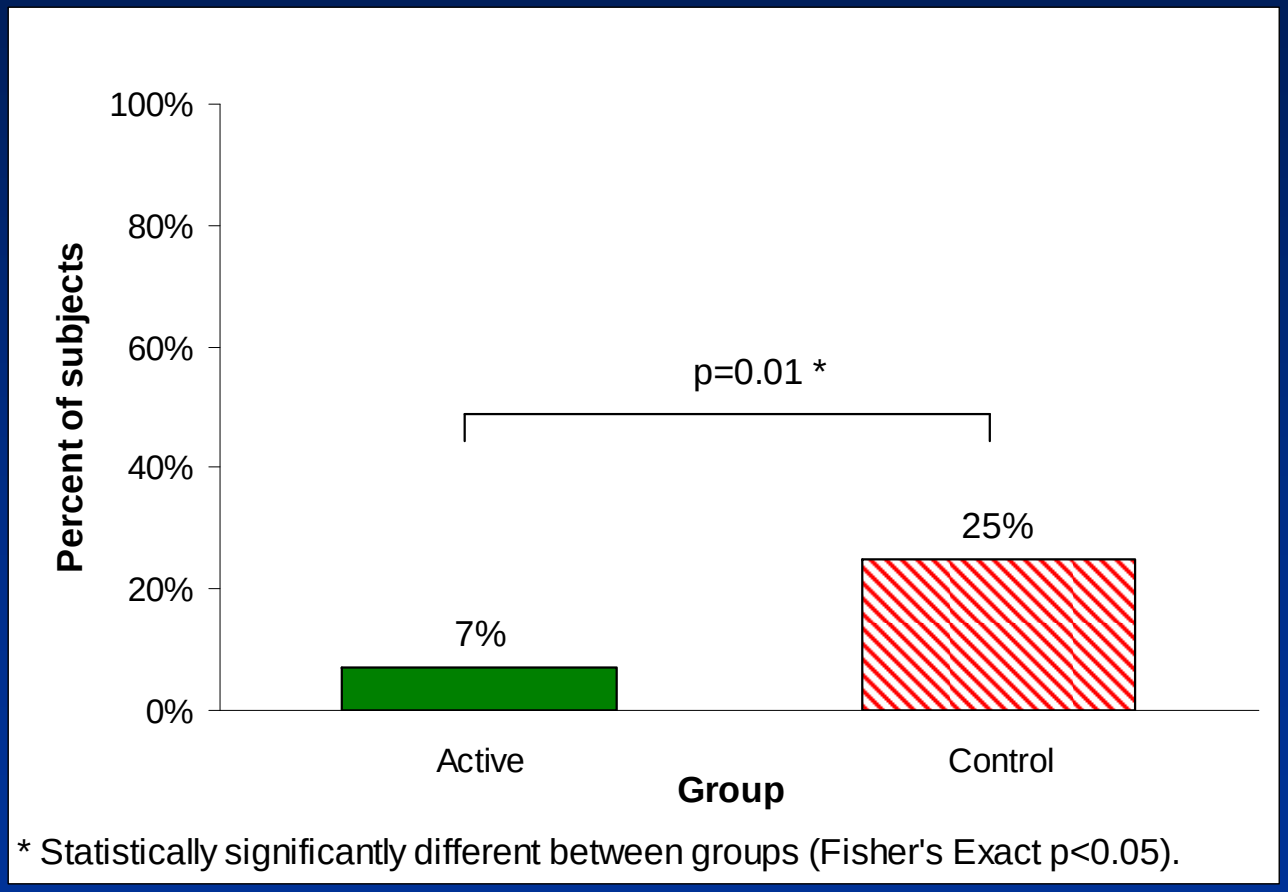
Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up



Epilepsy-Related Injuries

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

Persons with epilepsy are at a higher risk for incurring seizure-related accidental injury[a]



[a] Beghi et al, Epilepsia, 2002

Secondary Objectives and Additional Study Measures

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

	Active	Control	P-value
Secondary objectives			
Responder rate	**30%**	26%	ns
Seizure-free days	**15.3%**	8.8%	ns
Seizure-free intervals	**35.0%**	24.0%	ns
Treatment failure rate	0	0	ns
Additional study measures			
Liverpool seizure severity scale (neg is better)	**-8.2**	-6.8	ns
Most severe seizure	**-40%**	-20%	p<0.05
QOLIE-31 (positive is better)	2.5	**2.8**	ns
Satisfied with the therapy	55.5%	**69.2%**	ns
Access Therapy Controller use	**13.0**	16.0	ns
Healthcare resource utilization (hosp)	**0.02**	0.09	ns
Rescue medication use (mean number of uses)	**0.79**	2.27	ns

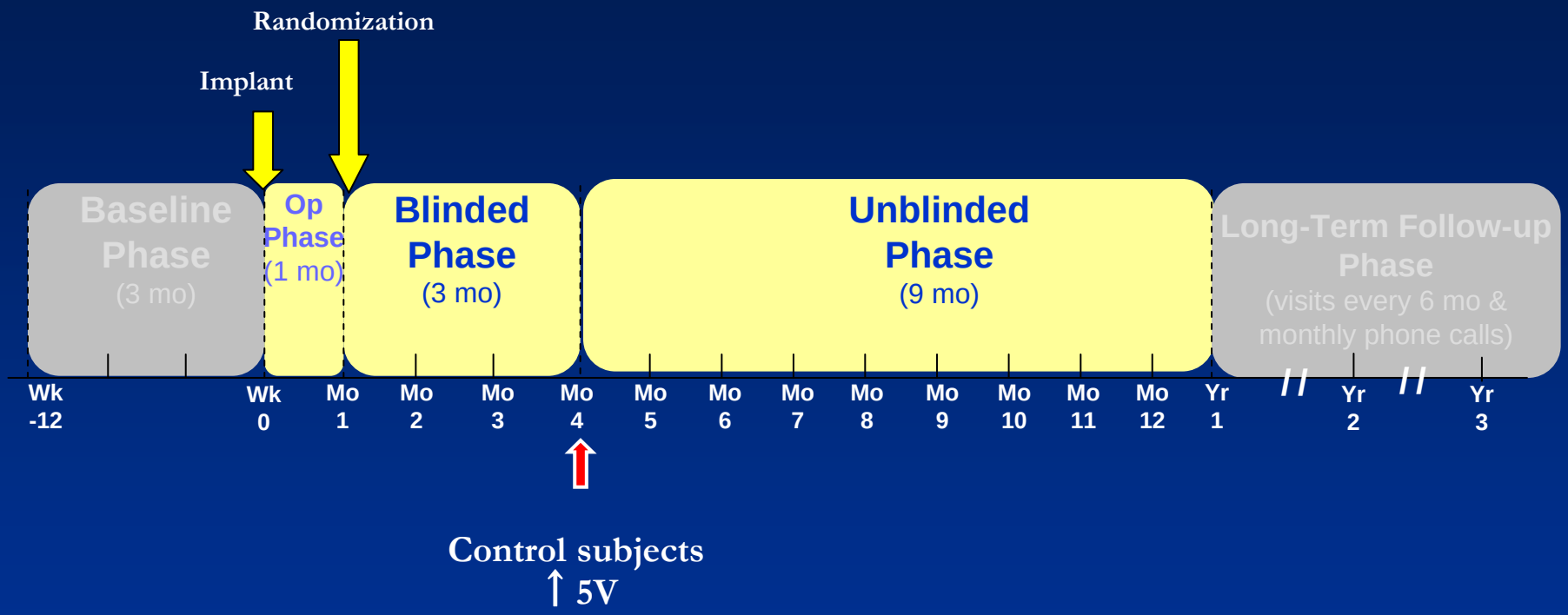
Yellow numbers indicate a trend towards benefit in the highlighted group.

Blinded Phase Efficacy Results Summary

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

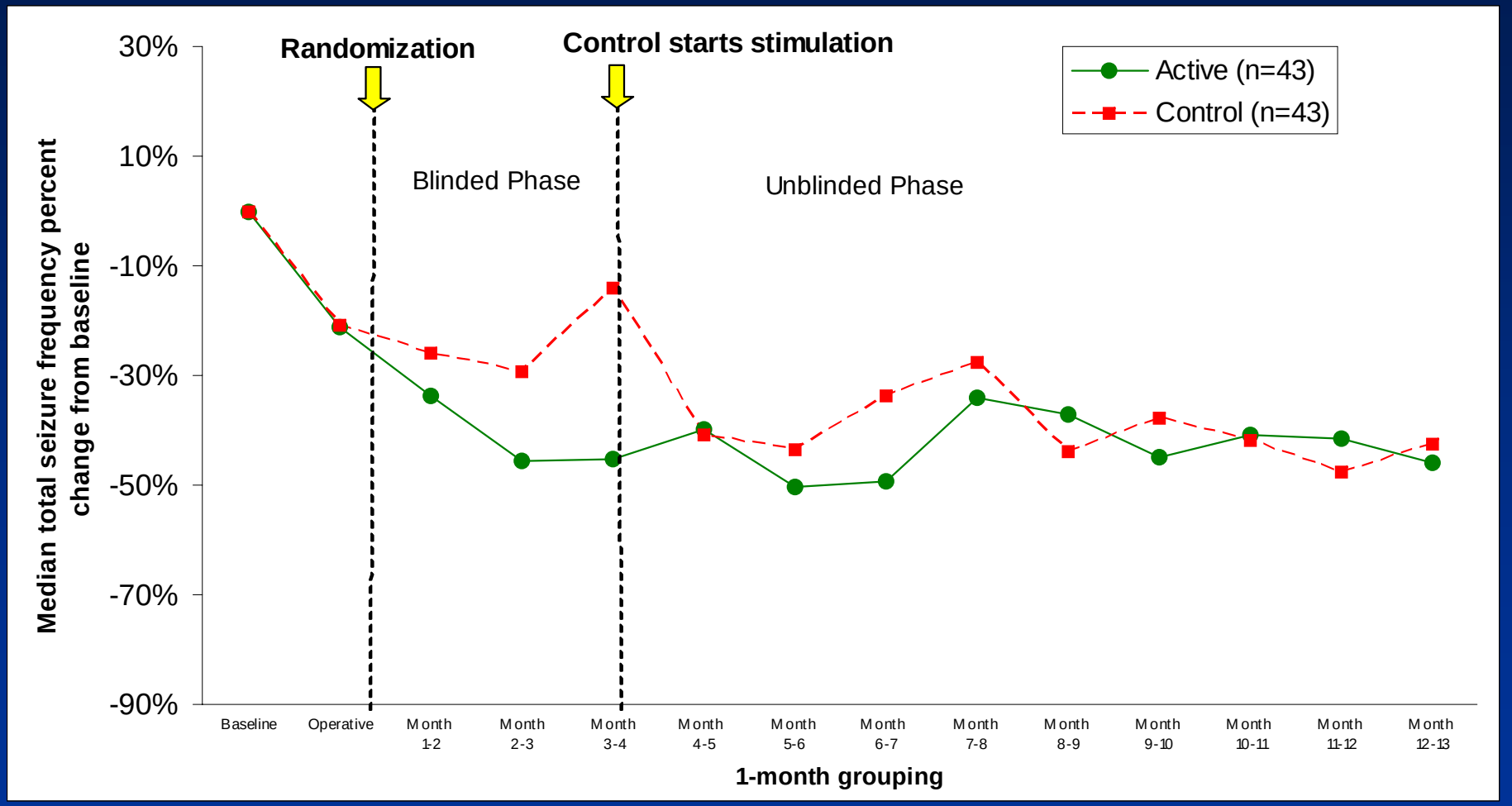
- A statistically significant reduction in the seizure rate was seen in the Active group compared to the Control group.
- 40% reduction in seizures is clinically meaningful in this population.
- Complex partial, “most severe,” and seizure related injuries were significantly less with stimulation.
- All analyses found a significant benefit for the active intervention in the final month of the Blinded Phase.
- These results provide a reasonable assurance of effectiveness.

Unblinded Phase



Seizure Frequency Reduction to 1 Year

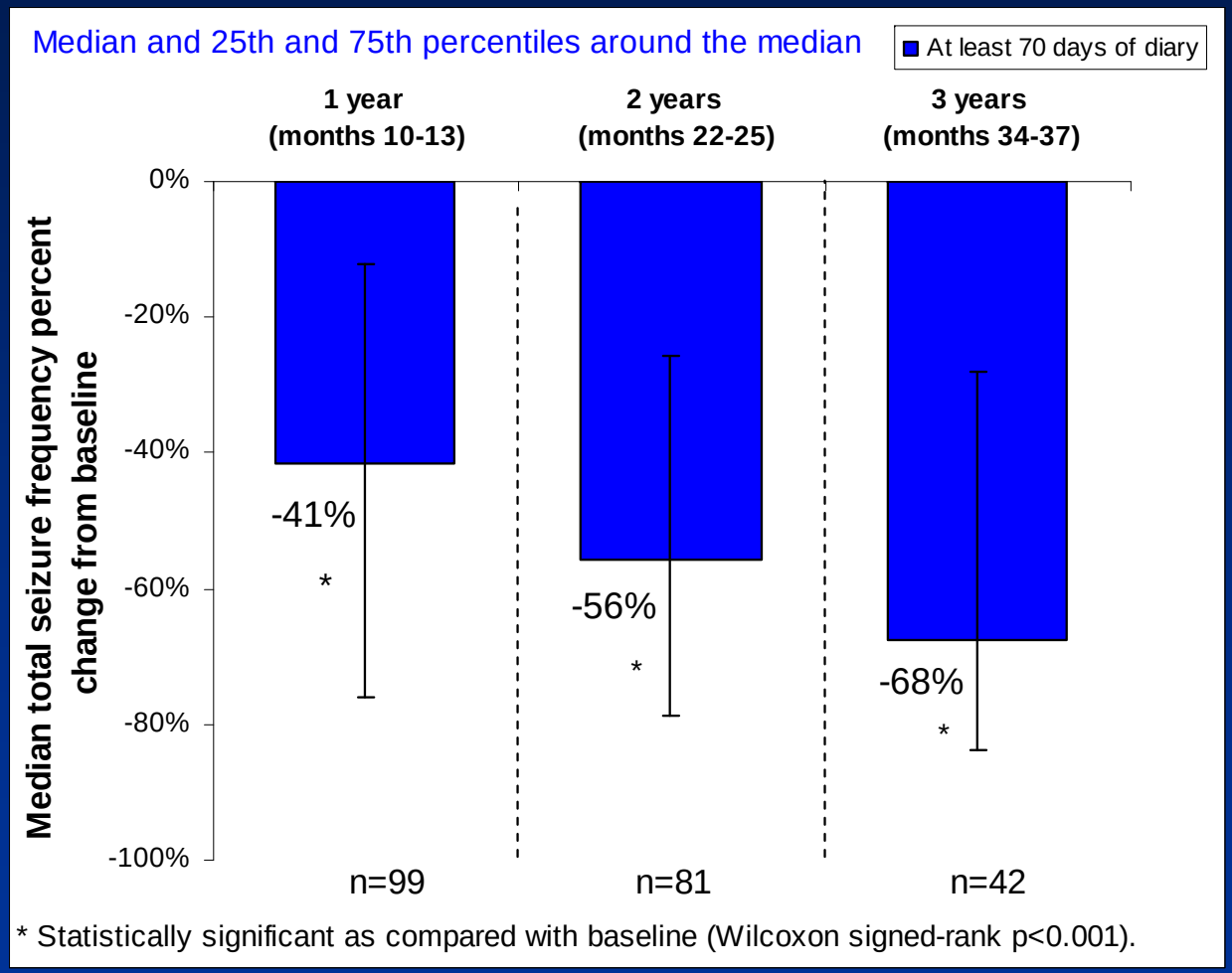
Baseline	OP	Blinded	Unblinded	Long-Term Follow-up



Includes subjects with at least 70 days of diary in each 3-month period (ie, Mo 1-4, Mo 4-7, Mo 7-10, and Mo 10-13).

Seizure Frequency Reduction

Baseline	OP	Blinded	**Unblinded**	**Long-Term Follow-up**

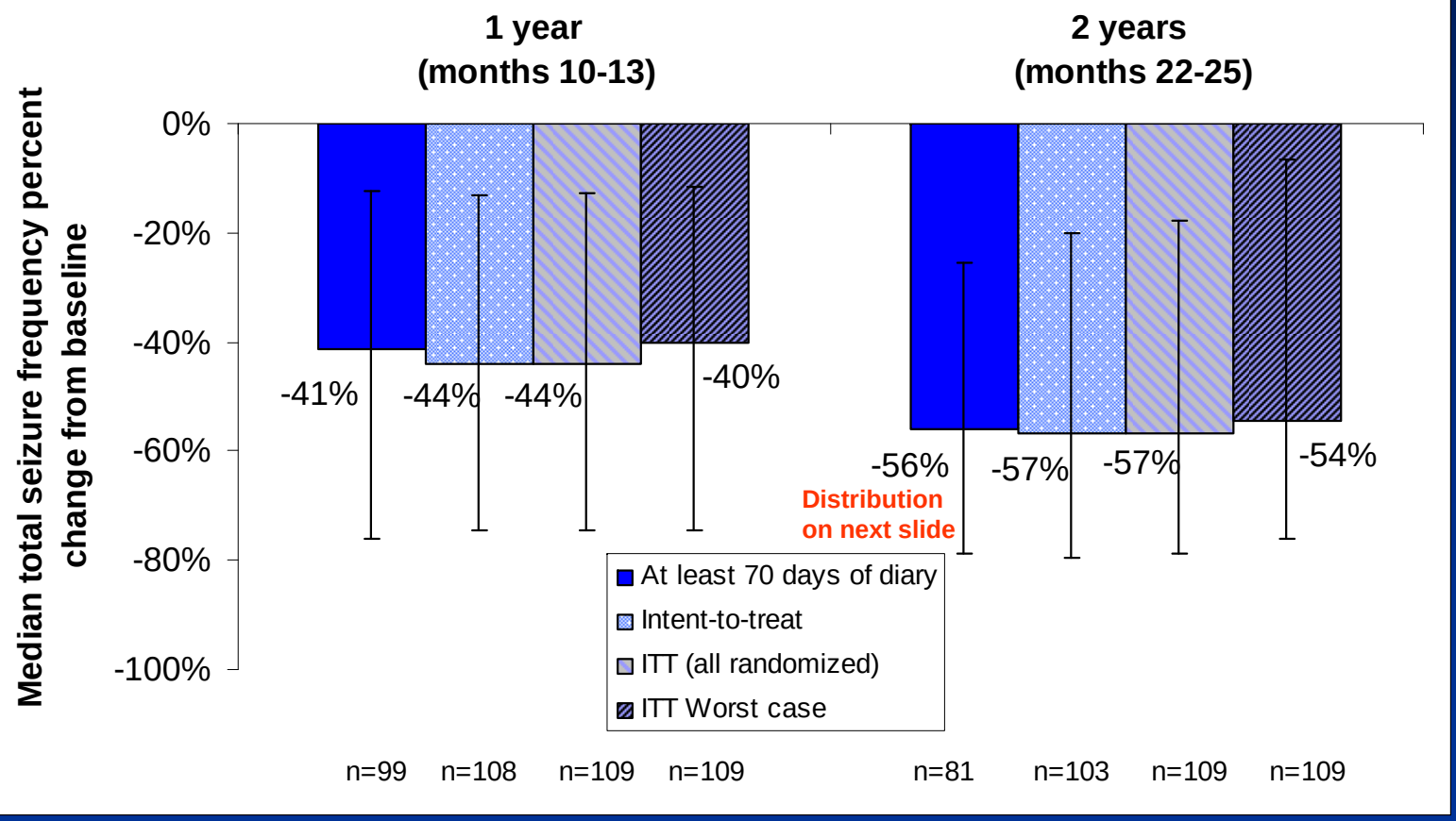


* Statistically significant as compared with baseline (Wilcoxon signed-rank p<0.001).

Seizure Frequency Reduction, ITT

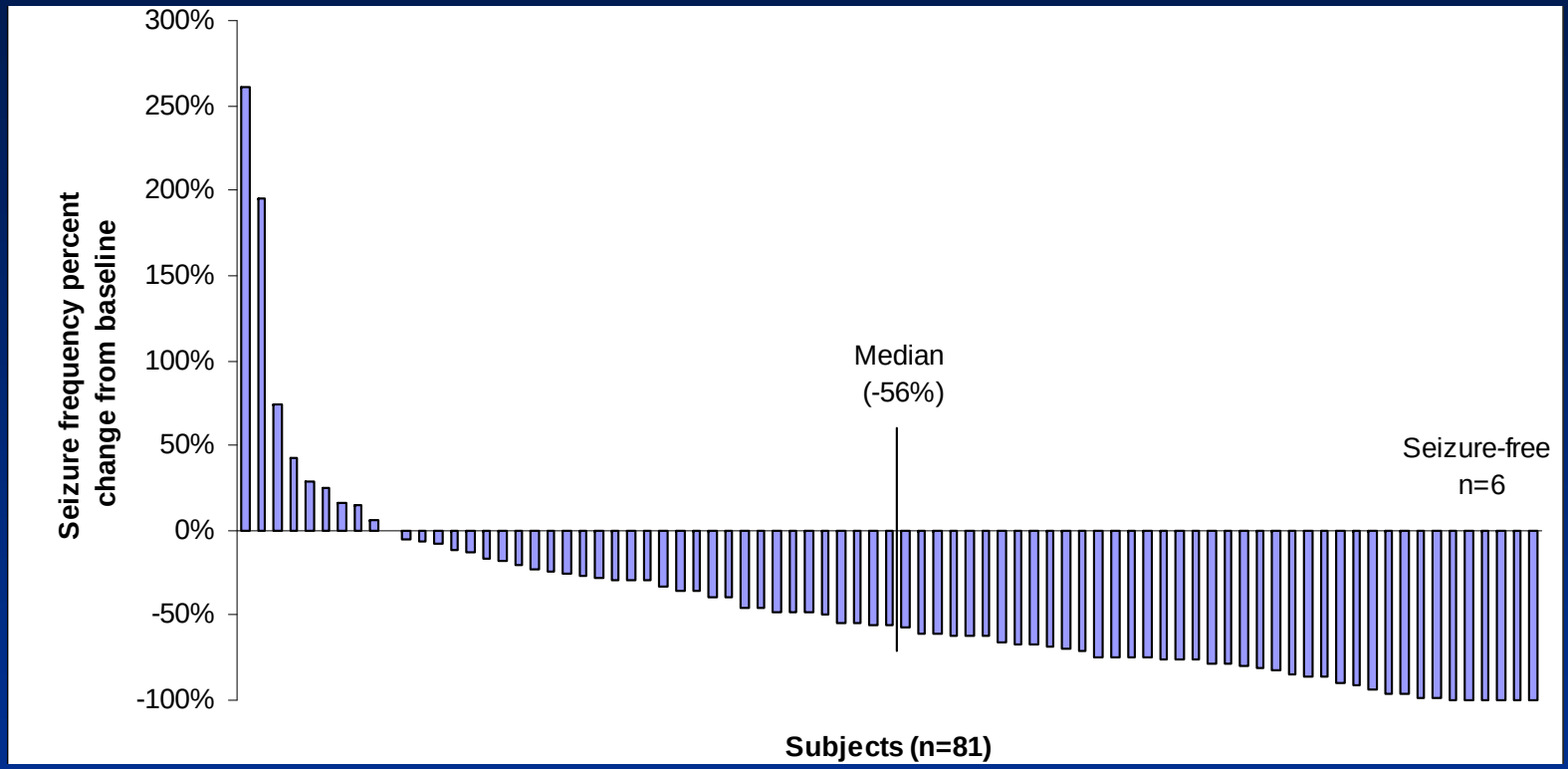
Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

Median and 25th and 75th percentiles around the median



Seizure Frequency Change at 2 Yrs (by Subject)

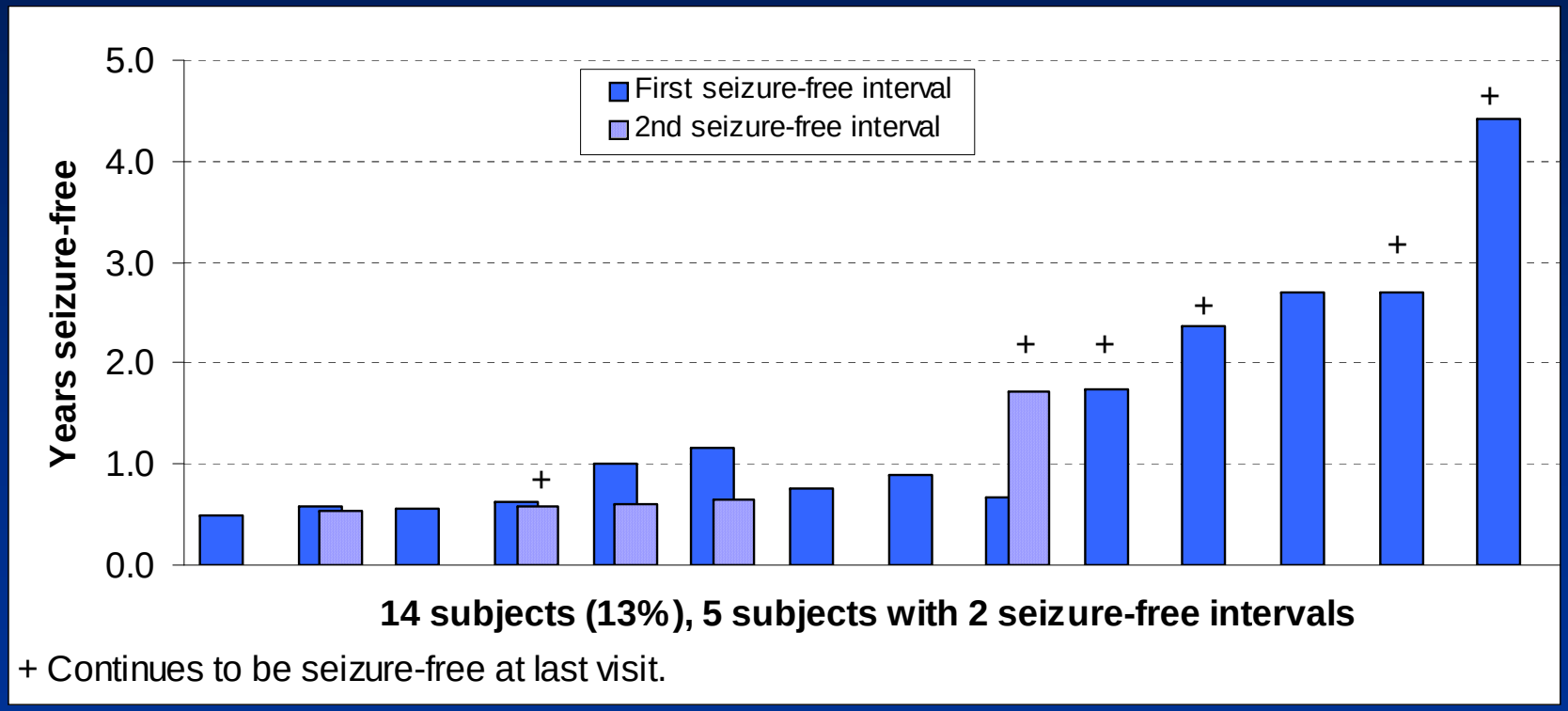
Baseline	OP	Blinded	Unblinded	Long-Term Follow-up



Subject No.	Overall: % change	Simple: % change	Complex: % change
AAA	266.0%	626.1%	-65.3%
CCC	194.9%	268.9%	0.1%
EEEE	73.7%	88.6%	-100%

Seizure-free for at Least 6 Months

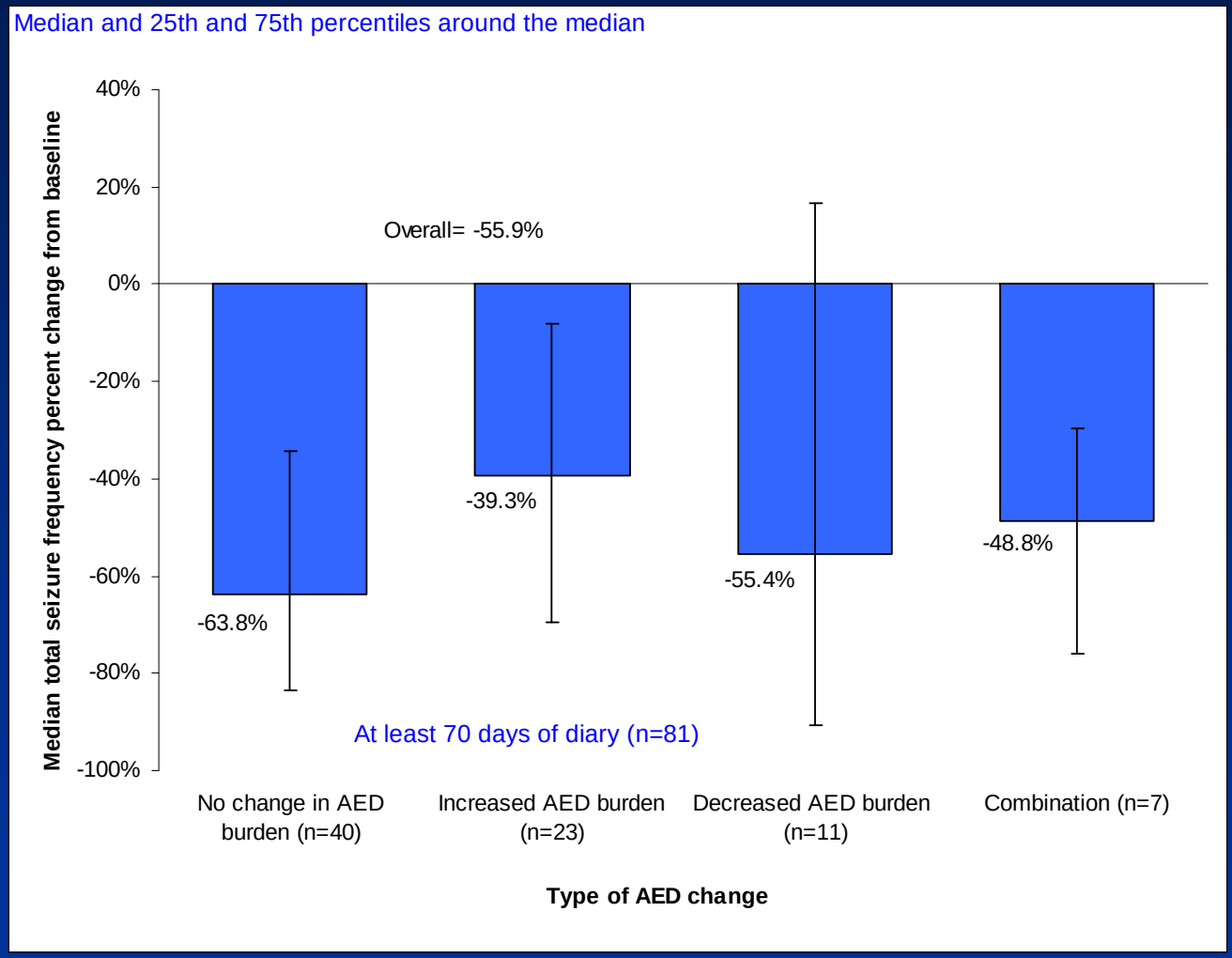
Baseline	OP	Blinded	Unblinded	Long-Term Follow-up



+ Continues to be seizure-free at last visit.

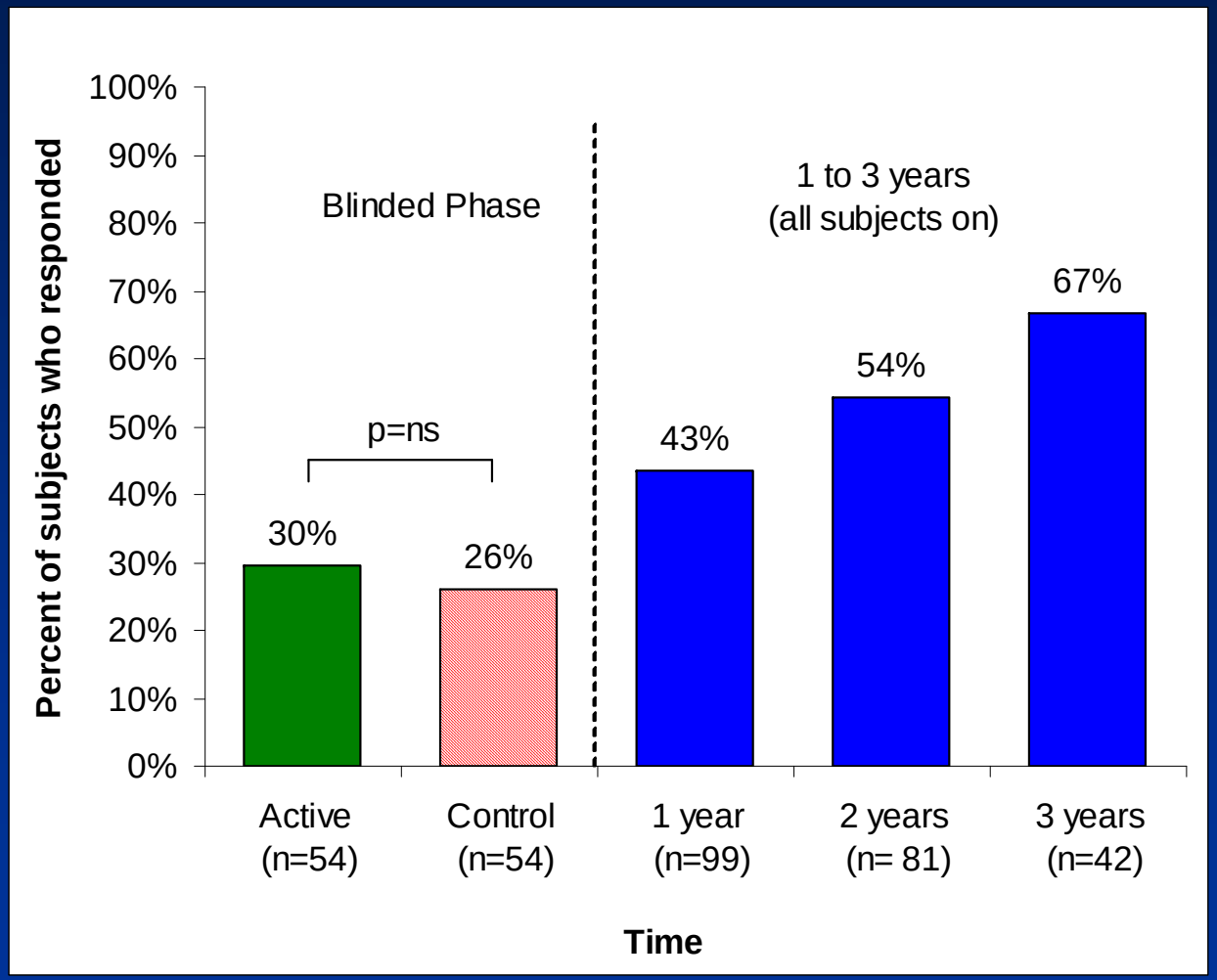
Antiepileptic Drug (AED) Usage at 2 Years

Baseline	OP	Blinded	Unblinded	**Long-Term Follow-up**



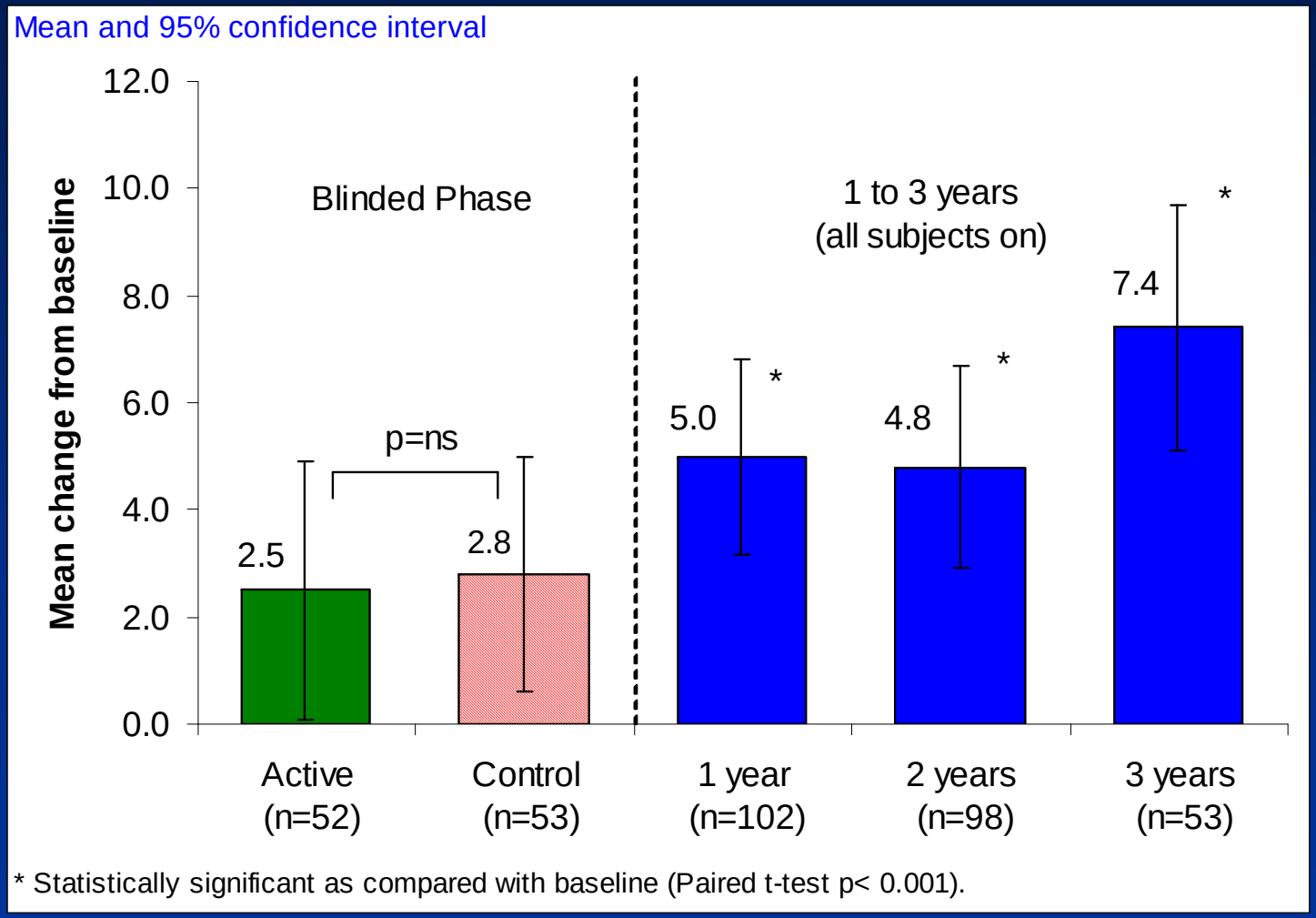
Responder Rate (≥ 50% reduction in total seizures)

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up



Quality of Life in Epilepsy-31

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up



Patient Satisfaction with the Therapy

At one year post randomization

1. Rate your overall satisfaction with the therapy (0-4 scale)
   - 74% reported being satisfied or greatly satisfied with the results of their therapy.
2. Considering your overall outcome with your therapy, and considering the operation(s), hospitalization(s), discomfort and expense involved, would you go through it all again for the same result?
   - 81% reported that they would go through the therapy again knowing the result.
3. Based on your experience, would you recommend this therapy to a friend with epilepsy similar to yours?
   - 88% would recommend it to a friend.

Efficacy Summary

- Blinded Phase
  - A statistically significant reduction in the seizure rate was seen in the Active group compared to the Control group.
  - 40% seizure reduction is clinically meaningful in this population
  - Complex partial, “most severe,” and seizure related injuries were significantly less with stimulation.
- Efficacy is maintained long term
  - 41%, 56%, 68% seizure reduction at 1, 2, 3 years
  - Quality of life and responder rate improve long-term
  - 13% of subjects were seizure-free for at least 6 months
- DBS therapy is efficacious in this patient population

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	**Robert S. Fisher, M.D., Ph.D.**
Post-Approval Plans	Nina Graves, PharmD
Study Conclusions	Robert S. Fisher, M.D., Ph.D.

Safety Objectives

- Characterize the adverse events experienced with the DBS system stimulating the ANT in subjects with refractory epilepsy

- Characterize the incidence of sudden unexplained death in epilepsy (SUDEP) with the DBS system stimulating the ANT in subjects with refractory epilepsy

Adverse Events Definitions

- All adverse events were categorized and reported by the Investigator according to the study protocol.
  - Seriousness
  - Severity
  - Causality (device, subject, or drug)
- All events were coded in the database with the MedDRA dictionary.
- All events were adjudicated by Clinical Events Committee (CEC) and reviewed by DSMB.

Blinded Phase Depression Events

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

- Self-reported worsening or new onset:
  - 14.8% (8/54) active
  - 1.8% (1/55) control

  ] p=0.02
- One of the events was serious
- All were mild or moderate, none were severe
- Depression resolved in half of the subjects
- Neuropsychological depression scores were unchanged or better in 5 of the 8 active subjects.

Unblinded and LTFU Depression Events

Baseline	OP	Blinded	**Unblinded**	**Long-Term Follow-up**

- The new reports of depression decrease over time
- None of the events were serious
- 23 were mild or moderate, 1 was severe
- Depression testing was unchanged or improved in 80% of these subjects at next testing

Event	**Unblinded Months 4-13 (n=108) no. (%)**	**LTFU**		
		Year 1-2 (n=105) no. (%)	**Year 2-3 (n=102) no. (%)**	**After Year 3 (n=57)**
Depression	11 (10.2%)	8 (7.6%)	3 (2.9%)	2 (3.5%)

Proposed Physician Labeling

- Warning:
  - Depression monitoring – During treatment, patients should be monitored closely for new or changing symptoms of depression.
- Patient counseling information:
  - Physicians should carefully monitor patients for new or changing symptoms of depression. Such symptoms may include a change in sleep or eating behavior.

Suicidality

- Incidence of suicidality events in implanted subjects (7.2% total) is less than published rates for other refractory epilepsy patients (12[a]-25%[b])

	Baseline *(3 mo)* n=157	Implanted subjects			
		Year 1 *(13 mo)* n=110	Year 1-2 (n=105) no. (%)	Year 2-3 (n=102) no. (%)	After Year 3 (n=57)
Suicidal ideation	1 (0.6%)*	2 (1.8%)	1 (0.9%)	1 (1.0)	1 (1.8%)
Suicide attempt	1 (0.6%)*	-	-	-	1 (1.8%)
Death by suicide	-	-	-	-	1 (1.8%)
Intentional self injury	-	-	1 (0.9%)	-	-
* Both subjects discontinued during the Baseline Phase					

[a] Jones et al 2003
[b] Tellez-Zentano et al, 2007

Suicide Details

- The subject was a 29 year-old male with long-standing depression
- At the last study visit (3 days before his death), stimulation was found to have been OFF for 3 weeks, due to battery depletion.
  - Subject had 1 seizure in that 3-week period.
  - A replacement procedure was being scheduled.
  - Subject had 2 prior episodes of battery depletion, where device was OFF for 3 weeks and 6 weeks.
- All POMS-D scores had been normal.
- The subject was recently divorced.
- The Investigator, CEC and DSMB have reviewed this event and do not believe it to be related to the DBS therapy, DBS withdrawal, or seizure rebound.

Blinded Phase Memory Impairment Events

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

- Self-reported worsening or new onset
  - 13.0% (7/54) active
  - 1.8% (1/54) control

  ] p=0.03
- None of the events were serious
- All were mild or moderate, none were severe
- All of the events resolved
- Neuropsychological testing of memory was stable in all subjects, and some showed improvement

Unblinded and LTFU Memory Impairment Events

Baseline	OP	Blinded	**Unblinded**	**Long-Term Follow-up**

- None of the events were serious
- All were mild or moderate, none were severe
- 53% of the subjects had unchanged or improved memory scores at the next evaluation

Event	**Unblinded Months 4-13 (n=108) no. (%)**	**LTFU**		
		Year 1-2 (n=105) no. (%)	**Year 2-3 (n=102) no. (%)**	**After Year 3 (n=57)**
Memory impairment	12 (11.1%)	2 (1.9%)	1 (1.0%)	5 (8.8%)

Neuropsychological Test Results

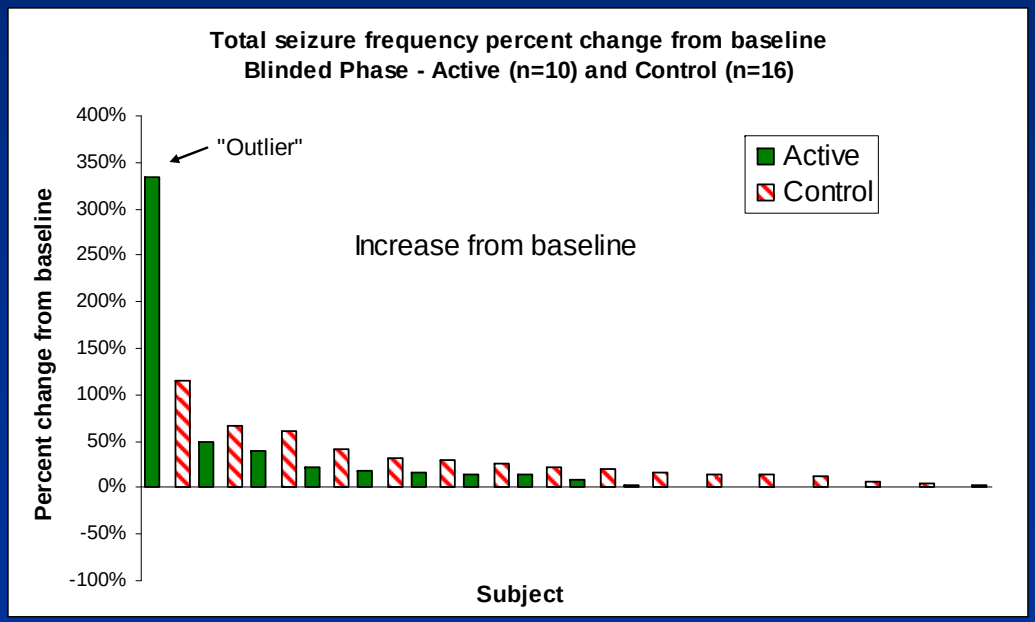
Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

- Baseline scores indicate mild impairment in attention, memory, and expressive language and mild depression, tension/anxiety, mood disturbance and confusion.
- Stable neuropsychological profile throughout the study:
  - Blinded Phase: no statistically significant differences between Active and Control groups for all tests
  - Long-term Follow-up Phase: a trend towards improving neuropsychological results

Increase in Seizures During Blinded Phase

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

- Some subjects had an increase in seizures
  - 10/54 active subjects
  - 16/54 control subjects
- With the exception of the outlier, all increases in the active group were <50% whereas 3 subjects in the control group had increases 50% -115%.



Seizures as Adverse Events

- Minimum requirements for reporting seizures as an adverse event:
  - New seizure type
  - Seizure(s) resulted in hospitalization or ER visit
  - Status epilepticus
- Investigators may, at their discretion, submit any seizure-related adverse events.

Seizure Adverse Events in Blinded Phase

Baseline	OP	**Blinded**	Unblinded	Long-Term Follow-up

- No statistically significant difference in seizure adverse events between treatment groups
  - Active: 2-9%, depending on seizure type
  - Control: 2-7%, depending on seizure type
- Most AE reports were generated due to:
  - New seizure type (SPS or CPS)
  - Hospitalization or ER visit
  - Increased seizure frequency due to AED non-compliance or low AED drug levels

Seizure AEs the First Week of Stimulation

	Day occurred (related to stimulation start)	Outcome
Blinded Phase		
Complex partial seizures (outlier)	Day 1	Resolved within 48 hrs of reprogramming
New simple partial seizure	Day 5	Ongoing, 4 total seizures of this type in study, through Mo 33
Unblinded Phase		
Confusion/status epilepticus	Day 1	Resolved within 1 day of reprogramming
Longer more intense simple partial seizure	Day 1	Resolved within 2 wks of reprogramming
Longer simple partial seizure	Day 1	Resolved within 1 day without intervention

Status Epilepticus

3 of the 5 subjects were not receiving stimulation at the time of the event

Phase reported	**Convulsive or Non-convulsive**	**Serious**	EEG Confirmation	**Timing of event**	**Receiving stim at the time of event?**
Operative	Non-convulsive	No	No	The day of the original implant procedure after missed AED dose	No
	Non-convulsive	Yes	Yes	1 wk after original implant procedure after missed AED dose	No
Blinded	Non-convulsive	Yes	No	Mo 2 (active subject)	Yes
Unblinded	Non-convulsive	Yes	Yes	The day of the mo 4 visit, when stimulation turned on (control subject)	Yes
LTFU	Convulsive	Yes	No	Between Mo 49 and 50	No[a]

[a] Stimulation was OFF for approximately 1 year at the time of the event

Proposed Physician Labeling

- **Precaution**
  - Patient monitoring – Seizure frequency may increase when stimulation is initiated. Adjustment of stimulation parameters may alleviate this effect. Instruct patients to carefully monitor their seizure frequency during the first few days and weeks after stimulation is initiated (Source: Information for Prescribers).
- **Stimulation parameters**
  - …If seizure frequency increases when stimulation is initiated, adjustment of stimulation parameters may alleviate this effect (Source: Proposed Clinical Summary)

Most Frequent Serious Adverse Events

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

- **Leads not in target**
  - Criteria for randomization included at least one lead contact within the target ANT
  - 8.2% (9/110) subjects required lead revision
    - 14/220 (6.4%) of leads
    - Rate similar to DBS for other movement disorders
  - All leads were successfully repositioned
- **Implant site infection**
  - 7.3% (8/110) subjects
    - Rate similar to DBS for other movement disorders
  - None were in the brain
  - 5 required partial or complete explant, 2 re-implanted

Summary of Deaths

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

- 5 subject deaths
- None were considered by the Investigator or DSMB to be device-related

Phase (last visit)	**Cause of Death**	**SUDEP Classification**
Baseline	SUDEP	Probable
Unblinded	SUDEP	Definite
LTFU	SUDEP	Definite
LTFU	Drowning	Possible
LTFU	Suicide	Not SUDEP

One additional death was reported after the database cutoff.

SUDEP Summary

- SUDEP rate is 5.0/1000 patient years
- Lower than published SUDEP rate of 9.3 in epilepsy surgical candidates reported by Dasheiff.

Source of data	No. of SUDEP*	Yrs with stim	SUDEP rate/1000 person-yrs
SANTE	2	325 years	6.1
Pilot Follow-up	0	72 years	0.0
Total	2	397 years	5.0

*As per pre-defined criteria, only definite or probable SUDEP occurring after implant were included.

If possible SUDEP is included, the rate is 7.6

Intracranial Hemorrhage Adverse Events

Baseline	OP	Blinded	Unblinded	Long-Term Follow-up

- 5 asymptomatic intracranial hemorrhage were detected radiologically:
  - 4 on the post-implant MRI or CT scan
  - 1 on CT scan after seizure-related fall (post-explant in LTFU Phase)
- None of the events were serious or required intervention.
- No neurological deficits were observed.

MRI on Patients with Previous VNS

- Labeling will reinforce most conservative of existing MRI use conditions for VNS and DBS:
  - VNS System – Complete explant or trim lead to ≤ 4 cm
  - DBS System – Head scan (send/receive) only
- No anticipated adverse effects
  - 49 prior VNS patients underwent MRI in the SANTE trial without injury
  - Follow DBS MRI scan limitations – RF energy exposure significantly less than that allowed for VNS

Safety Summary

- No unanticipated adverse device effects
- Depression and memory impairment reported more frequently in Active group patients
  - Stable neuropsychological testing profile
  - Depression monitoring is addressed in the labeling
- Seizures may occur upon initiation of stimulation and is addressed in the labeling
- No symptomatic intracranial hemorrhages
- SUDEP rate lower than reported in a similar population
- Procedural and hardware-related risks consistent with other DBS therapies

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Physician and Center Staff Training

- Medtronic Field support provides:
  - Center evaluation
  - Tutoring of surgeons at their home centers
- Medtronic Medical Education offers the following:
  - Introductory and advanced courses for clinicians
  - Traveling Nurse Program
  - Access to experienced neurosurgeons and managing physicians
  - Access to onsite training programs at experienced DBS centers

Post-Approval Studies

Medtronic has established the safety and efficacy of DBS therapy for epilepsy through the SANTE randomized controlled trial and through extensive clinical and commercial experience with the other DBS therapies.

Medtronic has identified the following 3 objectives for the post-approval phase:

- Continued characterization of long-term efficacy
- Continued characterization of serious adverse events and adverse events related to the device, implant procedure or therapy
- Characterization of therapy efficacy in open-label use, without restrictions on programming or AED usage

Excerpts from Physician Labeling

- Warning: Depression monitoring
- Precaution: Initiation of stimulation
- Precaution: Interactions between the DBS system and other implanted devices
  - System implant with abandoned VNS lead
- Patient Counseling information: Therapeutic effect

Excerpts from Physician Labeling

- Interactions between the DBS system and other implanted devices
  - Multiple implants – The long-term safety associated with multiple implants, leads left in place without use, replacement of leads, multiple implants into the target structure and lead explant is unknown. (Source: Information for Prescribers, Precautions section)
- System implant with abandoned VNS lead
  - Vagus nerve stimulation (VNS) – Refer to the manufacturer's instructions for explant of a VNS system prior to implanting a Medtronic DBS System for Epilepsy. (Source: Information for Prescribers, Precautions section)

Excerpts from Physician Labeling

- Therapeutic effect
  - Physicians should inform patients who are recipients of Medtronic DBS Therapy for Epilepsy that it may take time (perhaps several months or more) to achieve maximum therapeutic effect from the stimulation. Patients should be reminded that a seizure diary or seizure counting on the patient programmer are essential for the optimization of the therapy and should be considered a long-term commitment. (Source: Information for Prescribers, Patient Counseling Information section)

Presentation Overview

Epilepsy Background	Robert S. Fisher, M.D., Ph.D.
Study Design and Conduct	Nina Graves, PharmD
Patient Population	Robert S. Fisher, M.D., Ph.D.
Primary Objective Methods and Results	James Rochon, Ph.D. Evan Sandok, M.D.
Additional Efficacy Results	Robert S. Fisher, M.D., Ph.D.
Safety Results	Robert S. Fisher, M.D., Ph.D.
Post-Approval Plans	Nina Graves, PharmD
Conclusion	Robert S. Fisher, M.D., Ph.D.

Conclusion

- Refractory epilepsy is highly prevalent; new therapies are needed.
- Efficacy of the therapy was demonstrated in individuals with a long history of epilepsy who had tried and failed most other treatment options.
- Safety profile of DBS therapy acceptable compared to the significant consequences of continued seizures.